COMPREHENSIVE-HOLISTIC NEUROREHABILITATION,
OUTCOMES AND THEIR SUBJECTIVE APPRAISAL
IN ADULTS WITH TRAUMATIC BRAIN INJURY

Jaana Sarajuuri

ACADEMIC DISSERTATION
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Unigrafia, Helsinki 2020
To my Thai princess, Tsa Singphap
ABSTRACT

Traumatic brain injury (TBI) has a critical public health impact worldwide because of its high incidence, prevalence, and socioeconomic consequences. The common neuropathology following TBI contributes to a myriad of diverse interacting impairments in cognitive, behavioral, emotional, and motor functioning. Many people with TBI experience ongoing long-term, lifelong and also evolving symptoms that impact their general health, psychosocial outcomes, and overall well-being. Over the last three decades, standards of care, rehabilitation interventions, and research for TBI patients have developed, yet robust evidence for effective practices and evidence-based guidelines do not exist for most interventions. The effectiveness of postacute neuropsychologically oriented multidisciplinary comprehensive-holistic rehabilitation programs (CHRPs) in enhancing psychosocial adjustment and outcome has been supported by several studies, but controlled studies are scarce. Moreover, there is a shortage of research examining the associations between cognition and motor functions, particularly in patients with TBI, although such associations may have clinical implications for neurorehabilitation. Recently, awareness has increased of the need to supplement rehabilitation outcome assessment of TBI patients by subjective measures, which may have important implications for the allocation of different rehabilitation interventions and to enhance outcomes.

The studies of this thesis investigated the psychosocial outcomes of an application of CHRP (Study I) and the relationship between the objective outcomes and their subjective self-appraisals in adults with postacute TBI (Study III) as well as the association between cognitive and motor functions for benefits in multidisciplinary neurorehabilitation after TBI (Study II).

In Study I, the productivity of 19 consecutive adult patients with postacute moderate to severe TBI who underwent CHRP in a nationwide neurorehabilitation center setting was compared with that of 20 matched controls who received conventional clinical care and rehabilitation. After a six-week CHRP, the patients were followed up for two years and then evaluated for long-term outcome. The status of their productivity was judged as productive (defined as working, studying, or participating in volunteer activities) or nonproductive by two blinded and independent raters, and evaluated with structured questionnaires filled in by the patients and their significant others. In Study II, cognitive and motor functioning of 34 physically well-recovered men with postacute moderate to severe TBI was assessed. Cognitive functioning was measured in the domains of information processing, attention, and executive functions, particularly in regulation of
voluntary movements. Motor performance was measured in postural balance, agility, and gross motor rhythm coordination. Study III comprised 54 adults with chronic moderate to severe TBI who had resumed working at various levels of competence following CHRPs running in two neurorehabilitation centers in two countries. The objective outcome measure was the level of work competence that participants had attained postrehabilitation. The subjective outcome measure was participants’ subjective self-appraisal of their rehabilitation outcomes by rating six measures: effort during rehabilitation, meaning in life, productivity, acceptance, social life, and intimate relationships.

Study I showed that at the end of follow-up 89% of patients in the CHRP group were productive compared with 55% of controls. CHRP was found to be significantly predictive of a productive status at follow-up, and other factors did not explain the better productivity of the CHRP group. Moreover, the findings of Study III indicated that the levels of work obtained after a CHRP were not associated with the areas of subjective self-appraisals other than the ability to establish intimate relationships. Overall, the patients were found to be largely satisfied with the areas of wellness after CHRPs. The explorative Study II analyzing the relationship between cognitive and motor functions in postacute TBI found associations of measures of information processing, attention, and executive functioning with agility and dynamic balance. The fluency of information processing and executive functioning was reflected in the speed of walking/dynamic balance and running, and vice versa.

The present results give evidence that the CHRP approach improves outcomes for individuals with moderate to severe postacute TBI even many years after injury (Studies I and III). The findings support the presumption that CHRPs facilitate achievement of a successful outcome through establishing a meaningful and satisfactory life after TBI in the face of persisting deficits. In line with the few previous studies, the findings of Study II support the interplay between cognition and motor performance supporting the possible multimodal effects of TBI rehabilitation and encouraging use of comprehensive multidisciplinary neurorehabilitation to enhance outcomes. Finally, the results of Study III are consistent with earlier studies that have noted a dissociation between functional outcomes and subjective well-being, especially in chronic TBI. Community functioning and the related satisfaction seem to be distinct aspects of participants’ experience that must be considered in the evaluation of rehabilitation outcomes following TBI. These findings may have implications for rehabilitation service provision and allocation, encouraging a move towards CHRP models in rehabilitation of individuals with TBI to improve their psychosocial outcomes and subjective well-being.
TIIVISTELMÄ

Aivovammoilla on maailmalaajuisesti merkittävä vaikutus terveydenhoitoon niihin liittyvän korkean ilmaantuvuuden sekä sosioekonomisen taakan vuoksi. Aivovammoille ominaiseen neuropatologialle liittyy suuri määrä

erilaisia kognitiivisia, käyttäytymisen ja tunne-elämän sääteilyn sekä motorisen
toimintakyvyn häiriöitä. Ne aiheuttavat usein pitkäaikaisia, elinikäistä ja myös
ajan myötä kehittyvää toimintakyvyn alenemaa, mikä heikentää monen vam- 
mautuneen yleistä terveydentilaa, psykososiaalista toimintakykyä ja hyvinvointia. Vaikeka aivovammapotilaiden hoidon, kuntoutusinterventoiden ja tutkimuksen

laatu on viimeisten kolmen vuosikymmenen aikana kehitnyt, tehokkaiden

käytäntöjen tutkimusnäyttö on yhä vähäistä, eikä kuntoutusinterventioista ole

juurikaan näyttöön perustuvia suositksia. Aivovamman postakuutin vaiheen

kokonaisvaltaisten-holististen neuropsykologisesti painottuneiden moniammat-

illisten kuntoutusohjelmien (CHRPR) vaikuttavuutta potilaiden psykososiaalisen

toimintakyvyn kohdentamiseksi on osoitettu usealla tutkimuksella, mutta kont-

rolloitujen tutkimuksia on vähän. Puutetta on myös tutkimuksesta, joka selvit-

täisi kognitiivisten ja motoristen toimintojen yhteyksiä, vaikka näillä saattaisi

olla kliinistä merkitystä aivovammojen kuntoutuksessa. Viime vuosina on myös

lisääntynyt tietoisuus tarpeesta täydentää kuntoutuksen tuloksellisuuden arvi-

ointia kuntoutujan omakohtaiseen kokemukseen perustuvalla arvioinnilla, jolla

saattaisi olla merkitystä erilaisten kuntoutusinterventioiden kohdentamiseen.

Tässä väitöskutkimuksessa tutkittiin CHRPR-soveltujen vaikutusta aivovam-

mapotilaiden psykososiaaliseen toimintakyvyn (Osatutkimus I), kuntoutuksen

objektiivisesti mitattavien ja subjektiivisesti arvioitujen vaikutusten välistä

yhteyttä (Osatutkimus III) sekä kognitiivisen ja motorisen suoritumisen välisiä

yhteyksiä niiden hyödyntämiseksi kononaisvaltaisessa moniammatillisessa

aivovamman kuntoutuksessa (Osatutkimus II). Osatutkimus II vertasi 19 aikuis-

potilasta, joilla oli postakuutin vaiheen keskivaiketa tai vaikea aivovamma ja

jotka oli valittu peräkkäin kuuden viikon mittaiseen CHRPR-kuntoutukseen, ja

20 kontrollipotilasta, jotka olivat saaneet yleisen terveydenhuollon käytäntöjen

mukaisia kuntoutuspalveluja. Kahden vuoden seuranta-ajan jälkeen arvioitiin

potilaiden produktiivisuutta (työssä, opiskelemassa tai osallistumisen vapaa-

ehtoistyöhön) lopputulosmuuttujalla ’produktiivinen’ tai ’ei-produktiivinen’

kahden sokkoutetun arvioitsijan toimesta. Produktiivisuus arvioitiin struk-

turoidulla kysymyslomakkeella, jonka täyttävät potilaat ja heidän läheisenä.

Osatutkimus II mittasi 34 fyysisesti hyvin toipuneen postakuutin vaiheen

keskivaiketa tai vaikea aivovamman saaneen miehen kognitiivista ja moto-

rista toimintakykyä. Kognitiivista toimintakykyä arvioitiin tiedonkäsittelyn

sujuvuuden, tarkkaavuuden ja toiminnanohjauksen, erityisesti tahdonalaisten


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This study was conducted at the Faculty of Medicine, Department of Psychology and Logopedics, University of Helsinki, Finland. Financial support from the Ministry of Education, the Medical Fund of Helsinki and Uusimaa Hospital District, the Finnish Cultural Foundation, the Miina Sillanpää Foundation, the Finnish Association of People with Physical Disabilities, and the Käpylä Rehabilitation Centre is gratefully acknowledged.

The thesis was inspired by and completed alongside multidisciplinary clinical work with patients sustaining traumatic brain injury (TBI) with the goal of attending to patients within the therapeutic milieu by applying professional theory to effective practice. I am enormously grateful to the patients and their families who were willing to share their experiences and taught me so much. Working in this exciting field has taken me on an inspiring journey that has lasted three decades. Over the years, I have been fortunate to work with several talented, enthusiastic, and wonderful people.

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I am honored and grateful to Professor James Malec, a distinguished and voluminous researcher in neuropsychology and brain injury rehabilitation, for kindly agreeing to act as opponent in the public defense of my thesis. Professor Malec initially planned to travel from Maryland, USA to Helsinki to be present at the public discussion. However, due to the coronavirus pandemic, this was not possible. I also thank the pre-examiners of my thesis, the internationally eminent Professor Keith D. Cicerone and Docent Päivi Hämäläinen, a dedicated and skillful colleague. Your insightful perspectives and suggestions improved the summary of my dissertation immensely. I thank also my author-editor Carol Ann Pelli for fine work on revising the language of the thesis.

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Espoo, September 2020

Jaana Sarajuuri
“If one is truly to succeed in leading a person to a specific place, one must first and foremost take care to find him where he is and begin there. This is the secret in the entire art of helping... But all true helping begins with a humbling. The helper must first humble himself under the person he wants to help and thereby understand that to help is not to dominate but to serve, that to help is not to be the most dominating but the most patient, that to help is a willingness for the time being to put up with being in the wrong and not understanding what the other understands.”

Søren Kierkegaard in 1848; citation from Hong & Hong, 1998, p. 460
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<th>Abbreviation</th>
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<tbody>
<tr>
<td>AAN</td>
<td>American Academy of Neurology</td>
</tr>
<tr>
<td>ABI</td>
<td>acquired brain injury</td>
</tr>
<tr>
<td>ADL</td>
<td>activities of daily living</td>
</tr>
<tr>
<td>APOE</td>
<td>apolipoprotein gene</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CBI</td>
<td>chronic brain injury</td>
</tr>
<tr>
<td>CCT</td>
<td>computerized cognitive training</td>
</tr>
<tr>
<td>CDC</td>
<td>US Centers for Disease Control and Prevention</td>
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<tr>
<td>CERAD</td>
<td>Consortium to Establish a Registry for Alzheimer’s Disease</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>Chi-Square Test</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
</tr>
<tr>
<td>CR</td>
<td>cognitive reserve</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DAI</td>
<td>diffuse axonal injury</td>
</tr>
<tr>
<td>DI</td>
<td>diffuse injury</td>
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<tr>
<td>DTI</td>
<td>diffusion tensor imaging</td>
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<tr>
<td>ED</td>
<td>executive dysfunction</td>
</tr>
<tr>
<td>EF</td>
<td>executive function</td>
</tr>
<tr>
<td>GBD</td>
<td>global burden of disease</td>
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<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
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<tr>
<td>GOS</td>
<td>Glasgow Outcome Scale</td>
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<tr>
<td>GOSE</td>
<td>Glasgow Outcome Scale, Extended</td>
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<tr>
<td>GMR</td>
<td>geometric mean ratio</td>
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<tr>
<td>GRS-R</td>
<td>Coma Recovery Scale, Revised</td>
</tr>
<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
</tr>
<tr>
<td>INSURE</td>
<td>Individualized Neuropsychological Subgroup Rehabilitation</td>
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<tr>
<td>IQ</td>
<td>intelligence quotient</td>
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<tr>
<td>LNI</td>
<td>Luria’s Neuropsychological Investigation</td>
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<tr>
<td>LOC</td>
<td>loss of consciousness</td>
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<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>mTBI</td>
<td>mild TBI</td>
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<tr>
<td>N</td>
<td>normal</td>
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<tr>
<td>NA</td>
<td>not applicable</td>
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<tr>
<td>Abbreviation</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>NR</td>
<td>neuropsychological rehabilitation</td>
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<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>P</td>
<td>pathological</td>
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<tr>
<td>PTA</td>
<td>posttraumatic amnesia</td>
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<td>Q1</td>
<td>lower quartile</td>
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<td>Q3</td>
<td>upper quartile</td>
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<tr>
<td>QoL</td>
<td>quality of life</td>
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<tr>
<td>QOLIBRI</td>
<td>Quality of Life after Brain Injury Scale</td>
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<tr>
<td>QOLIBRI-OS</td>
<td>QOLIBRI Overall Scale</td>
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<tr>
<td>r</td>
<td>effect size</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>RPQ</td>
<td>Rivermead Post-Concussion Symptom Questionnaire</td>
</tr>
<tr>
<td>RTA</td>
<td>road traffic accident</td>
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<tr>
<td>RTW</td>
<td>return to work</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SE</td>
<td>standard error</td>
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<tr>
<td>SF-36</td>
<td>36-Item Short Form Health Survey</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
</tr>
<tr>
<td>STATA</td>
<td>software for statistics and data science</td>
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<tr>
<td>TPM</td>
<td>time pressure management</td>
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<tr>
<td>TBI</td>
<td>traumatic brain injury</td>
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<td>TBIMS</td>
<td>Traumatic Brain Injury Model Systems</td>
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<td>TMT</td>
<td>Trail Making Test</td>
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<tr>
<td>TRACK-TBI</td>
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<td>U</td>
<td>Mann-Whitney statistics</td>
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<td>WAIS-R</td>
<td>Wechsler Adult Intelligence Scale, Revised</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>YLL</td>
<td>years of life lost</td>
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1 INTRODUCTION

1.1 TRAUMATIC BRAIN INJURY (TBI)

1.1.1 DEFINITION AND DIAGNOSTIC CRITERIA

In recent decades, the definition of TBI has evolved reflecting the increased understanding of injury to the brain. The Lancet Neurology Commission (Maas et al., 2017) defines TBI as an alteration in brain function, or other evidence of brain pathology, caused by an external force (Menon, Schwab, Wright, & Maas, 2010). According to the explanatory notes, alteration in brain function is defined as one of the following clinical signs: any period of loss or decreased level of consciousness (LOC); any loss of memory for events immediately before (retrograde amnesia) or after the injury (posttraumatic amnesia, PTA); neurologic deficits (weakness, loss of balance, change in vision, dyspraxia paresis/plegia, sensory loss, aphasia, etc.); or any alteration in mental state at the time of injury (confusion, disorientation, slowed thinking, etc.).

Typically, TBI is diagnosed when the symptoms are closely temporally related to the insult. However, clinical manifestations of TBI may also be delayed (e.g. Bigler, 2013; Rabinowitz & Levin, 2014). A diagnosis of TBI may be dependent on diagnostic tests undertaken sometime after the acute event. In this context, other evidence of brain pathology may involve evidence such as neuroimaging, blood biomarkers, or neuropsychological assessment confirming damage to the brain. Finally, the definition caused by an external force may include any of the following events: the head being struck by an object; the head striking an object; the brain undergoing an acceleration/deceleration movement without direct external trauma to the head; a foreign body penetrating the brain; forces generated from events such as a blast or explosion; or other force yet to be defined. This definition is applicable across the continuum of injury severities and includes a wide range of injury mechanisms (Roozenbeek, Maas, & Menon, 2013).

1.1.2 EPIDEMIOLOGY

TBI has major public health and socioeconomic impacts worldwide (Maas et al., 2017; Rubiano, Carney, Chestnut, & Puyana, 2015). It is the most important cause of injury-related death and disability (Faul, Xu, Wald, & Coronado, 2010; Majdan et al., 2016, 2017; World Health Organization, WHO, 2006), although
consistent epidemiological data are lacking. TBI affects all ages, but especially young adults (Coronado, McGuire, Faul, Sugerman, & Pearson, 2012; Rozenbeek et al., 2013). An estimated 50 to 60 million people worldwide sustain a new TBI each year (Feigin et al., 2013): 10 million of these cases lead to mortality or hospitalization (Langlois, Rutland-Brown, & Wald, 2006). In the United States of America, 3.5 million new TBI cases have been reported to occur annually (Coronado et al., 2012), of which about 2.5 million are admitted to hospital (Taylor, Bell, & Breiding, 2017), with 53 000 deaths (Coronado et al., 2012). In the European Union, the estimated annual number is at least 2.5 million (Maas et al., 2017), of which about 1.5 million are treated in hospital and 57 000 die (Madjan et al., 2016).

Annual incidence rates for TBI vary substantially across the world and between countries (Centers for Disease Control and Prevention, CDC, 2015; Feigin et al., 2013; Majdan et al., 2016). In Europe, two meta-analyses (Brazinova et al., 2016; Majdan et al., 2016) have reported hospitalized and fatal TBI incidence rates of 262 and 287 per 100 000 per year. However, only an estimated 25% of all TBI cases are treated in hospitals (Sosin, Sniezek, & Thurman, 1996). Moreover, up to one-fourth of individuals sustaining a TBI may not seek medical attention (Coronado et al., 2011). The number of patients who receive medical care but have undiagnosed TBI is not known (Langlois, Rutland-Brown, & Wald, 2006). Data for TBI prevalence are even more limited than data for incidence (Maas et al., 2017) due to unreliable findings and scarcity of studies (Tenovuo, Bulloch, & Zafonte, 2012). The global prevalence of TBI in 2016 was estimated to be 55.5 million cases in the recent Global Burden of Disease (GBD) study (James et al., 2019). A meta-analysis of 15 studies (Frost, Farrer, Primosch, & Hedges, 2013) showed that 12% of adults had sustained a TBI with LOC, with men being at more than double the risk of women. A birth cohort study in Sweden showed that about 9% of the cohort had sustained TBI by the age 25 years (Sariaslan, Sharp, D’Onofrio, Larsson, & Fazel, 2016).

In general, road traffic accidents (RTAs) and falls are the most important causes of TBI (Brazinova et al., 2016; Majdan et al., 2016). The changing epidemiology of TBI shows an increase towards pediatric and elderly populations, mainly due to falls, in high-income countries (Brazinova et al., 2016; CDC, 2015; Koskinen & Alaranta, 2008; Peeters et al., 2015). In low- and middle-income countries the rising incidence is attributable to RTAs primarily affecting young people (Maas et al., 2008). TBI is anticipated to remain the leading global cause of neurological disability at least until 2030 representing a two to three times higher cause than Alzheimer’s disease or cerebrovascular disorders (WHO, 2006).
1.1.3 PATHOPHYSIOLOGY OF TBI

Initiated by an external mechanical impact, TBI comprises a biomechanical response with multiple pathophysiological processes that develop over time in a continuum (e.g. Rashid, Destrade, & Gilchrist, 2013; Stocchetti & Zanier, 2016). The resulting injury response in tissue and the clinical manifestation in individual patients are affected by multiple properties of the mechanical impact such as type (direct or indirect; linear-translational, rotational, or angular), mode, extent, duration, velocity, and loading histories; size, mass, and hardness of the impacting object; and material properties of the tissue (e.g. Bilston, 2011; Cloots, van Dommelen, Kleiven, & Geers, 2013; Jin, Zhu, Mao, Shen, & Yang, 2013; Prange & Margulies, 2002; Sack et al., 2009). The dominant pathophysiological processes can vary between patients depending on preinjury factors, coagulation status, and systemic responses; within patients over time; and between different parts of the brain across time (Maegle et al., 2017). Thus, TBI patients demonstrate dissimilar levels of harm and every case is novel with specific recovery profiles (Kaur & Sharma, 2017).

According to current understanding of the physiological response to TBI, damage from brain injury occurs in two phases (Morley, 2018). The direct loading at the time of injury causes the primary injury which is characterized by the initial axonal shearing, hemorrhage, and tissue damage (Greve & Zink, 2010; Park, Bell, & Baker, 2008). The second, neurochemically based phase begins at the time of injury evolving for days, weeks, months, or even over a lifetime in some cases (Dashnaw, Peterlaia, & Bailes, 2012; Greve & Zink, 2010; LaPlaca et al., 2007; Park et al., 2008) and results in the secondary brain injury including a cascade of interacting pathophysiological processes. The initial reaction to TBI is an immune response whereby microglial activation is followed by glutamate and calcium flux with impaired homeostasis, neuronal excitotoxicity, lethal metabolic changes, free radical generation, mitochondrial dysfunction, and energy crisis, which leads to progressive and delayed axonal disconnection and neuronal death (Akinrinade, Memudu, Ogundele, & Ajetunmobi, 2015; Greve & Zink, 2010; Kaur & Sharma, 2017; Morley, 2018; Stein, 2013). The accumulation of brain injury increases expression of amyloid precursor protein, which may lead to more severe neuropathological and neurobehavioral changes after a repetitive mild TBI (mTBI) than with a single TBI (Gao et al., 2017). Postmortem studies after TBI have shown complex persisting and evolving pathologies best described as polyopathy, including tau and amyloid Aβ abnormalities, neuroinflammation, white matter degradation, continued axonal degeneration, and neuronal loss (Hay, Johnson, Smith, & Stewart, 2016; Smith, Johnson, & Stewart, 2013). Similarly, a neuroimaging study review (Bigler, 2013) demonstrated prolonged
pathological changes, a loss of overall brain connectivity that progressively occurs even during the chronic phase.

Loadings to the brain can induce diffuse or focal neuropathologic processes that often coexist and contribute to the morbidity after TBI (e.g. Bigler & Maxwell, 2011; Povlishock & Katz, 2005). Due to the complex head and neck dynamics an external loading commonly exposes the brain to high linear and/or rotational acceleration and deceleration causing diffuse injury (DI) (Gayzik, Koya, & Davis, 2018; Hurst, Atkins, & Dickinson, 2018; Tierney & Simms, 2017) that includes diffuse axonal injury (DAI) and diffuse microvascular damage (Bigler & Maxwell, 2011; Liu, Kou, & Tian, 2014; Morley, 2018). Microvascular damage has been shown to be strongly involved in DAI at all severity levels of TBI, leading to dysfunction of adjacent neurons and disconnection between the cortex and subcortical structures (Glushakova, Johnson, & Hayes, 2014; Irimia, Van Horn, & Vespa, 2018; Liu, Kou, & Tian, 2014). DAI is also a common pathophysiological process in focal injuries along the severity continuum of TBI (Liu, Kou, & Tian, 2014; Morley, 2018; Sundman, Doraiswamy, & Morey, 2015), when both the strains and strain rates exceed 10% and 10/s, respectively (Rashid et al., 2013). Typically, DAI takes place at locations where there are changes in the direction of axons or the tissue density (Gaetz, 2004). DAI robustly correlates with neuropsychological dysfunction, poor long-term outcome, and decreased quality of life (QoL) (Aertker, Supinder, & Cox, 2016; Morley, 2018; Park et al., 2008).

Most focal injuries after TBI result in contusions at both the site and the contralateral site of impact, cerebral hemorrhages, and subdural and epidural hemorrhages (Bigler & Maxwell, 2011; LaPlaca, 2007; Povlishock & Katz, 2005). The mechanisms of acceleration–deceleration injuries in TBI often cause damage to the prefrontal areas (Pang, 1985), anterior and inferior temporal areas, and limbic neocortical and heteromodal areas of the frontal and temporal lobes, contributing to the common deficits in cognitive, behavioral and affective functioning (Bigler & Maxwell, 2011; Yetes, Levin, & Ponsford, 2017). The clinical sequelae related to focal injuries are often merged with the effects of DI (e.g. Wallesch, Curio, Galazky, Jost, & Synowitz, 2001). Following TBI, swelling may also occur, causing increased intracranial pressure that shifts brain structures or weakens cerebral blood flow, leading to ischemia and deficiency of oxygen to the brain (Maas et al., 2017).

The microstructural injury related to TBI is usually invisible with conventional computed tomography (CT) and magnetic resonance imaging (MRI) techniques, although patients with DAI may manifest marked disabilities (Morley, 2018). More advanced imaging techniques, such as diffusion tensor imaging (DTI), can probe the microscopic structure of white matter and detect its abnormalities
A current trend in TBI imaging research is to study network dysfunction when interpreting the neural mechanisms of cognitive and behavioral deficits (Sharp, Scott, Leech, 2014; Yetes et al., 2017). A continuous decrease in the integrity of multiple white matter tracts has been shown to be a long-term result following mild to severe TBI (Aertker et al., 2016; Wang et al., 2011).

1.1.4 RECOVERY AFTER TBI

*Concepts of neuroplasticity related to recovery and outcome in TBI.* Accumulated evidence demonstrates that neuroplasticity and recovery are possible after brain injury (e.g. Chen, Cohen, Hallett, 2002; Stein, 2013; Weishaupt, 2017). However, the underlying molecular or physiological mechanisms responsible for neuroplasticity remain largely unclear (Nagendran et al., 2017; Stein, 2013). It has been challenging to identify which of the neuroplasticity changes are adaptive in mediating recovery and which are maladaptive, resulting in permanent impairments or evolving neurological consequences (Chen et al., 2002; Stein, 2013; Wilson et al., 2017). Spontaneous reorganization as a result of the resolution of acute neurological events results in partial functional recovery (Chen & D’Esposito, 2010; Galetto & Sacco, 2017). The following neuroplastic reorganization is explained by unmasking of latent synapses and formation of new connections (Chen et al., 2002; Nudo et al., 2013; for review, see Wen, Shen, & Chen, 2017). Long-term changes may include mechanisms such as long-term potentiation (Hess & Donoghue, 1994), axonal regeneration, and sprouting with synaptogenesis (Kaas, 1991; Nagendran et al., 2017).

Genetic factors are assumed to modulate TBI recovery, partly accounting for the marked variability in recovery and outcome after apparently similar TBIs (for recent review, see Kurowski et al., 2017). Cognitive reserve (CR) has also been proposed to account for the disconnect between apparently similar TBIs and their level of clinical handicap (Hylin et al., 2017; Nunnari et al., 2014). Large CR has been suggested to serve as a preventative compensatory mechanism and to be associated with greater functional recovery after injury (Hylin et al., 2017; Schneider et al., 2014), whereas lower CR has been thought to exacerbate the secondary effects of TBIs (Fay et al., 2010). A recent review (Morley, 2018) conceptualized that one’s susceptibility to injury can be viewed on a continuum of brain resilience: optimal resilience at one end, characterized by a low neuroimmune state or resting microglia, capable of triggering efficient responses for recovery, and at the other end, diminished resilience, characterized by chronic primed microglia and hyperreactivity to injury with diminished...
capacity to recover. Modulating factors that impact physiological states in the brain are assumed to impact one’s brain resilience and efficacy of recovery (Morley, 2018).

**Implications of neuroplasticity to therapeutic treatments and rehabilitation.** Evidence of neuroplasticity has encouraged research on potential therapeutic treatments to modify plasticity, promote post-TBI repair and restrict secondary damage to decrease disability in TBI (e.g. Aertker et al., 2016; Bondi et al., 2014; Werner & Stevens, 2015). Neuroplasticity is also a common element in different rehabilitation approaches (Galetto & Sacco, 2017). Activating brain networks has been observed to be an effective way to promote plastic changes in healthy and in injured brains (Weishaupt, 2017). Cognitive rehabilitation has shown its efficacy to induce neural reorganization in chronic TBI regardless of severity of injury (Galetto & Sacco, 2017). This is assumed to diminish the maladaptive neuroplastic mechanisms that lead to accelerated aging, atrophy, and white matter changes, often seen in the chronic stages of TBI (e.g. Galetto & Sacco 2017; LaPlaca et al., 2007).

An essential question in the neurorehabilitation research is whether functional improvement after brain injury is based on true recovery or the development of compensation for lost functions (Galetto & Sacco 2017; Caplan et al., 2015). Research suggests that functional improvement viewed as changes in behavior or neuroplasticity interact with each other in a mutual way following injury (Hylin et al., 2017). Timing and intensity of rehabilitation, among other factors, have been found to have an impact on the efficacy of rehabilitation. It has been suggested that immediately after injury there is a vulnerable term during which rehabilitative training can reduce neuroplasticity and impair recovery (Griesbach, Gomez-Pinilla, & Hovda, 2004). Current research suggests that the ideal time to benefit from plasticity and behavioral outcome in rehabilitation is early on, but not immediately after central nervous system injury (Hylin et al., 2017). Rehabilitation intensity may also need to exceed a certain threshold to recover function and produce improvements (Hylin et al., 2017). High-intensity rehabilitation appears to be the most beneficial for gaining rehabilitation goals (Krakauer, Carmichael, Corbett, & Wittenberg, 2012).

**Prolonged recovery after TBI.** The natural recovery time of TBI has been shown to be potentially prolonged than that of most other acquired brain injuries (ABIs) (Katz, Zasler, & Zafonte, 2013; Walker et al., 2018). Current longitudinal follow-up studies suggest that improvements, but deteriorations as well, are common for many years – even up to two decades – after TBI (Corrigan & Hammond, 2013; Green, 2015; McMillan et al., 2012). However, systems of care are still
called for to follow patients during the protracted recovery time in TBI (Wilson et al., 2017).

TBI has to some extent a predictable course of cognitive, behavioral, affective, and sensorimotor deficits across the recovery period which is important to appreciate in targeting rehabilitation appropriately (Katz et al., 2013). A discernible pattern of neurobehavioral recovery of TBI across the continuum of severity from acute to chronic stages shows a transitioning through phases of alteration of consciousness, posttraumatic confusion and amnesia, and postconfusional recovery of cognitive functions (Katz et al., 2013). The behavioral deficits after TBI often proceed from deficits in arousal to basic attention and PTA to more complex attention, memory, and executive functioning, speed of information processing, self-awareness, and social awareness (Stuss & Buckle, 1992). Recovery after brain injury is seldom complete based on the findings on the long-term neuropathology after TBI (Bigler, 2013; Hay et al., 2016) and on the notion that plasticity is firmly controlled in the mature central nervous system (Weishaupt, 2017). However, growing evidence in neuroplasticity highlights the potential of interventions in facilitating recovery and adaptation for years after TBI (Malec et al., 2013; Ponsford et al., 2014; Wilson et al., 2017).

1.1.5 CLASSIFICATION OF SEVERITY AND IMPLICATIONS FOR OUTCOME

Sensitive methods for TBI and accurate measurement of TBI severity are vital to assist rehabilitation management in individual cases, establish the responsible party for treatment, avoid misclassification, allocate resources rationally, develop effective prevention, and improve clinical trials (e.g. Bitonte, Tribuzio, Hecht, & DeSanto, 2015; CDC, 2015; Dikmen, Machamer, & Temkin, 2017). Current classification systems are based on clinical observations of an injured patient’s brain functionality, and therefore, two patients classified as having the same TBI severity might have entirely different outcomes (Roebuck-Spencer & Cernich, 2014). Growing understanding of the vast number of pathophysiological processes with varying time frames in TBI has had important implications for the clinical assessment to conceptualize TBI severity (e.g. Maas et al., 2017).

The initial severity of TBI lies along a continuum, but has conventionally been classified as mild, moderate, or severe based commonly on the depth of altered consciousness as measured by the Glasgow Coma Scale (GCS) score (Teasdale & Jennett, 1974). However, classification based on GCS has proven to be unrefined and not to reflect different pathophysiological features of TBI (Maas et al., 2017). The length of LOC has also been used as an index of TBI severity, but has been proven to be less reliable because of differences in measurement (e.g. Ponsford, Spitz, & McKenzie, 2016)
Duration of PTA has evolved as a robust index of TBI severity and a standard practice in the management of TBI (e.g. Walker et al., 2018). PTA represents the period of time from injury until return to continuous memory for day-to-day events (Nakase-Thompson, Sherer, Yablon, Nick, & Trzepacz, 2004; Russell & Nathan, 1946). In addition to anterograde amnesia, PTA typically includes impairment in both memory storage and retrieval (Marshman, Jakabek, Hennessy, Quirk, & Guazzo, 2013). Amnesic period can also include islands of intact memory, which can be mistaken for the end of PTA (Russell & Nathan, 1946). Symonds and Russell also warned (1943, p. 7) that "... it is erroneous to assume that because a patient is aware of what is happening around him now he will be able to recall this later". Longer PTA durations have been associated with more severe TBIs and longer recovery times (e.g. Kosch, Browne, King, Fitzgerald, & Cameron, 2010; Ponsford et al., 2016). Both prospective and retrospective methods of assessing PTA have been confirmed to be valid measurements when compared systematically (McMillan, Jongen, & Greenwood, 1996). However, a lack of consistency exists regarding valid criteria for duration intervals of PTA to classify injury severity, hence several different criteria have been proposed (Jennett & Teasdale, 1981; Nakasa-Richardson et al., 2009 and 2011; Russell & Smith, 1961; Stein, 1996). In a recent study by Ponsford and colleagues (2016) the greatest accuracy in prognosis was achieved using continuous measures of PTA duration.

Of all TBIs, around 70–90% are considered mild (Faul et al., 2010; Maas et al., 2017; Tellier et al., 1999). However, there is currently no consensus-based criteria for defining mTBI (Dikmen et al., 2017; Maas et al., 2017), and current diagnostic measures may not identify affected individuals (e.g. Bitonte et al., 2015). Since 2009, there has been an increasing trend towards differentiating between mild-uncomplicated and mild-complicated injury (Hulkover et al., 2013). In most studies, complicated mTBI patients compared with uncomplicated ones have been reported to have a worse neuropsychological outcome (e.g. Papoutsis, Stargatt, & Catroppa, 2014). However, a multicenter cohort Transforming Research and Clinical Knowledge in TBI study (TRACK-TBI, https://tracktbi.ucsf.edu/) showed that independent of complicated or uncomplicated mTBI status at the one-year follow-up about 20–30% of patients were functionally impaired, over 80% remained symptomatic, and about 40% had significantly reduced well-being (McMahon et al., 2014). Recently, Livny and colleagues (2017) with premorbid neuropsychological data found cognitive decline in mTBI patients compared with healthy controls. Demographic and clinical variables at baseline are shown to explain less than 20% at best of the total variance in mTBI outcome (Cnossen et al., 2017).
Heterogeneity of TBI leads to inaccuracy in the classification of TBI as mild, moderate, or severe. Each of the severity indicators may be influenced by factors unrelated or indirectly related to TBI severity (Malec et al., 2006). Moreover, associations between GCS, LOC and PTA have been shown to be only moderate in strength (Sherer, Struchen, Yablon, Wang, & Nick, 2008). Recently, the Lancet Neurology Commission (Maas et al., 2017) remarked that current TBI diagnosing is inadequate to enable optimal treatments to individual patients. Increasing recognition exists that objective diagnosis of TBI should not be restricted to a single source of TBI-related information, but should be multifaceted (Bitonte et al., 2015; Irimia et al., 2017; Maas et al., 2017) also to improve outcomes (Ponsford et al., 2016; Vespa et al., 2014). Prospects to improve TBI characterization are currently evolving from advances in genomics (e.g. Failla, Conley, & Wagner, 2016), biomarkers (e.g. Kevin et al., 2018), high-resolution neuroimaging techniques (e.g. Wallace, Mathias, & Ward, 2018), and pathophysiological monitoring (e.g. Needham et al., 2017), together with developments in neuroinformatics (Schmidt et al., 2014).

The traditional severity indicators appear to have limited usefulness in classification of postacute TBI and guiding rehabilitation (Sherer et al., 2017). Initial injury severity has not been found to be strongly associated with the severity of the deficit sequelae in the postacute phase (Rabinowitz & Levin, 2014). As already known, many preinjury factors, comorbid conditions, and environmental supports can moderate recovery, manifestation of the postacute symptom profile, and outcome (e.g. Keenan, Clark, Holubkov, Cox, & Ewing-Cobbs, 2018; Seagly, O’Neil, & Hanks, 2017). Sherer and colleagues (2015) have initiated a large multicenter study to develop an approach for classifying postacute TBI. Recently, Sherer and colleagues (2017) identified five groups of postacute TBI patients who differed in clinically reasonable ways on the following dimensions: cognitive processing speed, memory, verbal fluency, self-reported cognitive symptoms, independence and self-esteem, resilience, emotional distress, postconcussive symptoms, physical symptoms, physical functioning, economic and family support, and performance validity. This methodology can be considered as an important preliminary step towards a more fine-tuned tool for conceptualizing postacute TBI severity and handicap and for planning rehabilitation.

Traditional severity indices of TBI have also shown a limited predictive power for cognitive outcomes and functional recovery in the acute phase (de Oliveira Thais et al., 2014). In turn, neuropsychological assessment at the acute stage has revealed a positive predictive power regarding disability, functional independence, and level of supervision (e.g. Hanks et al., 2008) and in identifying those in need of rehabilitation after TBI (Hacker et al., 2017). It strongly predicts
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productivity outcomes after TBI at the acute stage, being superior to other adjusted predictors of outcome such as PTA, preinjury education and preinjury employment status (Sherer et al., 2002).

As evidenced by a wide body of research (e.g. Sandel & Collins, 2018; Sherer et al., 2017; Soble, Critchfield, & O’Rourke, 2017), neuropsychological assessment should be a routine procedure in the postacute stage of assessing and treating TBI, as it is in the diagnostic process (e.g. American Academy of Neurology [AAN], 1996; Edidin & Hunter, 2013; Pearce et al., 2015). The AAN has designated the strongest recommendation level based on high confidence in the evidence for neuropsychological assessment to evaluate the cognitive and neurobehavioral effects of TBI (AAN, 1996, information current as of May 2013; Gronseth, Cox, Gloss, Dittman, & Armstrong, 2017). Mayo and colleagues (2019) highlight the need for neuropsychologists to ensure that they possess the necessary professional competency, training, and expertise to perform a comprehensive neuropsychological assessment for a patient with a TBI given the diversity of clinical manifestations and the far-reaching impact that the assessment may have on the patient’s rights and life (AAN, 1996; Moberg & Shah, 2012).

1.1.6 NEUROPSYCHOLOGICAL SEQUELAE OF TBI

Cognitive, behavioral, and emotional symptoms are often the most consistent and major concern in all types of TBI (Humphreys, Wood, Phillips, & Macey, 2013; Rabinowitz & Levin, 2014; Zasler, Douglas, & Zafonte, 2012). They have complex interactions (e.g. de Oliveira-Souza, Moll, & Grafman, 2011), occur in various combinations, and vary widely in their nature and severity, depending on the types and extent of the TBI as well as on the premorbid characteristics of the injured individual (Ponsford, Sloan, & Snow, 2013). Neuropsychological outcomes in TBI patients have been found to be significantly related to regional volumetric loss in white and gray matter structures (Livny et al., 2017; Spitz et al., 2013) and regions of altered function on DTI with all severities (for recent meta-analyses, see Zhang et al., 2019; Wallace et al., 2018), as well as to cerebral abnormalities in structural neuroimaging and cerebral blood flow (e.g. Fontaine, Azouvi, Remy, Bussel, & Samson, 1999; Ichise et al., 1994; Vilikki, Holst, Öhman, Servo, & Heiskanen, 1992).
Fatigue and sleep disturbances interact with cognitive, behavioral, and emotional deficits

Fatigue is among the most common symptoms experienced following TBI of all severities (e.g. for recent review, see Zuzuárrregui, Bickart, & Kutscher, 2018) both in the early stages of recovery (Rao et al., 2008) and the long term, even lifelong (e.g. Ponsford et al., 2012, 2013; Quellet & Morin, 2006). Typical features of pathological fatigue after TBI are a depletion of mental energy when there is a sensory overload and a disproportionately long recovery time to restore energy levels after mental exhaustion (Johansson & Rönnbäck, 2009). The proportion of fatigue after TBI varies considerably with reported prevalence ranging from roughly 30% to as high as 98% (Englander et al., 2010; LaChapelle & Finlayson, 1998; Quellet & Morin, 2006; Riese et al., 1999). Problems with fatigue have been reported to increase significantly over the first post-TBI year (Powell, Machamer, Temkin, & Dikmen, 2001).

Fatigue following TBI has been suggested to result from a number of factors. Primary fatigue may result from damage to brain centers that control arousal, attention, and response speed (Chaudhuri & Behan, 2004). Further, more extensive neural circuits are reported to be used in TBI patients during a given mental activity (Kohl, Wylie, Genova, Hillary, & Deluca, 2009), which contributes to a greater effort in performing tasks (e.g. Ziino & Ponsford, 2006). Potential secondary causes of fatigue have been reported to include sleep disturbances, pain, and emotional factors (Ponsford et al., 2012; Quellet & Morin, 2006). However, TBI itself has been proposed to make a unique contribution to fatigue (Cantor et al., 2008).

Sleep complaints are reported by 30–80% of patients with TBI (Mathias & Alvaro, 2012; Parcell, Ponsford, Rajaratnam, & Redman, 2006). These may include insomnia, hypersomnia, daytime somnolence, altered sleep-wake cycles, and specific complaints such as nightmares and early awakenings (Mathias & Alvaro 2012; Ponsford et al., 2012). Although most of the brain regions, pathways, and neurotransmitter systems associated with sleep regulation and the ascending reticular activating system are vulnerable to TBI (Bauman, Werth, Stocker, Ludwig, & Bassetti, 2007), causes of sleep disturbances after TBI seem to be multifactorial, including increased slow-wave sleep and disrupted circadian regulation of melatonin synthesis, reducing rapid-eye-movement sleep. Injury to histaminergic neurons and loss of melanin-concentrating hormone and orexin have been found to contribute to increased sleep need after TBI (Valko et al., 2015). Secondary factors include emotional distress, depression, and pain (Cantor et al., 2012; Shekleton et al., 2010). However, when anxiety and depression have been controlled, poor sleep quality was found to be associated with factors beyond mood disturbances (Shekleton et al., 2010).
While fatigue and sleep disturbances interact with one another and with changes in neuropsychological and motor performance, they have broader impacts on outcome in TBI (for review, see Singh, Morse, Tkachenko, & Kothare, 2016). Persisting fatigue and sleep problems can constrain day-to-day living, affect the ability to engage in domestic activities or manage at work, reduce energy for leisure activities, and impair long-term QoL (e.g. Beaulieu-Bonneau & Morin, 2012; Cantor et al., 2012; Willmot, Ponsford, Downing, & Carty, 2014). Fatigue has been reported to make a special contribution to disability in TBI after controlling for other factors, including depression and injury severity (Juengst, Skidmore, Arenth, Niyonkuru, & Raina, 2013).

**Cognitive impairments**

Cognitive difficulties caused by TBI are common, even in the mildest injuries (e.g. Rabinowitz & Levin, 2014). It is well established that yet minor changes in the ability to attend, process, recall, and act upon information can profoundly affect an individual’s daily functioning (National Institutes of Health [NIH], 1999). Rehabilitation outcomes and long-term effects of TBI on personal and psychosocial functioning can often be related to the integrity of cognitive abilities along with behavioral and emotional adjustment (Eslinger, Zappala, Chakara, & Barrett, 2012).

Attentional difficulties have been reported by more than 60% of moderate to severe TBI patients as long as ten years postinjury (Carroll et al., 2004; Olver, Ponsford, & Curran, 1996; Ponsford et al., 2014). Difficulties in complex attentional tasks have been shown to largely account for slowed information processing speed (Felmingham, Baguley, & Green, 2004; Ponsford & Kinsella, 1992), which has consistently been found to be reduced in TBI across injury severities (Dymowsky, Owens, Ponsford, & Willmott, 2015). Given the neuropathology, TBI can disrupt all components of attention such as arousal, speed of information processing, selective attention, and executive control of attention (Ponsford, Bayley, et al., 2014). DAI frequently disrupts attentional neural networks, including catecholaminergic and serotonergic pathways, whereas injury to the frontotemporal region and midbrain affects the reticular activating system (Povlishoch & Katz, 2005; Willmot, Ponsford,Hocking, & Schönberger, 2009). Abnormality in involuntary attention in chronic TBI with normal MRI is indicated by mismatch negativity, an event-related brain potential assumed to be associated with increased distractibility due to the loss of neural integrity (Kaipio, Cheour, Öhman, Salonen, & Näätänen, 2013).
TBI may alter the reaction time, the speed and accuracy of basic sensory-perception and perceptual-motor responses in several ways. It has been shown to slow the sensory detection and integration processes critical for timely and consistent responses (Eslinger et al., 2012). Deficits occur particularly with increasing task complexity, information load, and fatigue, leading to inconsistent, slowed, and erroneous responses (Stuss et al., 1989). Prolonged reaction times even in simple cognitive tasks have been reported also after mTBI (e.g. Piponnier et al., 2016).

TBI and memory appear to be intrinsically linked, as the hippocampus and prefrontal cortex, significant brain regions involved in memory functions, are typically injured in TBI (Paterno, Folweiler, & Cohen, 2017). Memory impairments are among the most frequent and often particularly salient and persisting after TBI (e.g. Paniak, Shore, & Rourke, 1989; Vanderploeg et al., 2014). Current literature reflects deficits in working (for meta-analysis, see Dunning, Westgate, & Adlam, 2016), episodic, and semantic memory (Tulving & Markovitch, 1998). However, deducing which memory phases – encoding, maintenance, or retrieval – are especially affected after TBI has been challenging (Paterno et al., 2017). Impaired episodic autobiographical memory has been associated with severe TBI (Coste et al., 2015; Esopenko & Levine, 2017), whereas results in mild to moderate TBI have been mixed (Barry & Tomes, 2015; Palombo et al., 2015). A recent meta-analysis showed that TBI patients demonstrate also lower prospective memory performance than controls (Gonzalez & Buchanan, 2019).

Based on the common neuropathology of TBI, executive function (EF) impairments are one of the most characteristic (Tate et al., 2014). White matter volume loss has been suggested to be a superior predictor of recovery and clinical outcome in functions involving broad networks such as EFs (Cristofori et al., 2015). Persisting executive dysfunction (ED) has been reported by up to 45% of moderate to severe TBI patients (Ponsford, Downing, et al., 2014). Deficits in EFs may also disrupt the ability to effectively use intact functions and undermine efficient self-management (Lewis, Babbage, & Leathem, 2011). TBI patients often have difficulties in analyzing, planning, and executing solutions to problems or checking for and correcting errors, although they may perform well in structured activities and in each component of a task. Moreover, they often show a lack of initiative or flexibility in their behavior and thought processes, lose track of the task, respond too strongly to distractions, or fail to use past experience to prepare for anticipated events or adapt to new situations (Busch, McBride, Glenn Curtiss, & Vanderploeg, 2005; Lezak, Hovieson, & Loring, 2004; Ponsford et al., 2013; Ponsford, Downing, et al., 2014). A difficulty in perceiving one's own deficits after TBI appears to be common in patients with ED (e.g. Arnould & Dromer, 2016; Fleming & Onsworth, 2006; Malec & Moessner, 2001). Sherer
and colleagues (1998) found that 76–97% of postacute TBI patients showed some degree of impaired self-awareness. EF impairments have been found to be associated with poorer long-term functional and psychosocial outcomes (e.g. Draper & Ponsford, 2008; Spitz, Ponsford, Rudzki, & Maller, 2012).

Commonly occurring communication impairments after TBI (Ponsford et al., 2013) generally reflect various underlying cognitive deficits such as slowed information processing, and deficits in attention, working memory, and EFs (Togher et al., 2014). Difficulties with word-finding, auditory processing, and naming appear to be typical persisting problems (Kerr, 1995; Levin, Grossman, & Sarwar, 1981). Primary language impairment, as in aphasia, can also result from TBI, but they are rare (Sarno, Buonagaro, & Levita, 1986). TBI patients have been described in communication as overtalkative, tangential, rigid, adynamic, inaccurate, perseverative on topics, and manifesting frequent interruptions or disinhibited responses (e.g. Togher et al., 2014). They may also show reduced conversational fluency, difficulties in interpreting abstract language, poor conceptualization and planning, and overall poor control of cognition and behavior in communication (Douglas, 2010; Togher et al., 2014).

The common neuropathology following TBI enhances also the likelihood of difficulties in social cognition skills, that is, the capacity to attend to, recognize, and interpret interpersonal cues (Bigler & Maxwell, 2011; Kennedy et al., 2009; McDonald, Honan, Kelly, Byom, & Rushby, 2014). Numerous studies (e.g. for meta-analysis, see Babbage et al., 2011) have indicated deficits in recognizing emotions following TBI. Moreover, studies have shown that empathy is reduced unrelated to TBI severity, time since injury, or co-existing cognitive deficits (e.g. de Sousa, McDonald, & Rushby, 2012; Williams & Wood, 2010), and is associated with high distress in caregivers (Wells, Dywan, & Dumas, 2005). Competence in social communication and social cognition skills after TBI are major predictors of psychosocial outcomes (e.g. Ponsford et al., 2013; Togher, McDonald, Tate, Power, & Rietdijk, 2009).

**Behavioral and emotional disorders**

The neuronal circuits that modulate complex emotional expression and behavior through complex excitatory and inhibitory pathways employing multiple transmitters (Bonelli & Cummings, 2007) overlap with brain regions vulnerable to TBI (McAllister, 2013). Behavioral and emotional symptoms are reported to be common and sustainable over time regardless of the TBI severity (for systematic review, see Stéfan & Mathé, 2016). Manifestations of these disorders are related to a complex and dynamic interaction between neurobiological, personal, social, and environmental factors relative to each person with TBI (Ciurli, Formisano,
Behavioral and emotional disorders are often characterized as flatness of affect with reduced emotional responsiveness, or conversely, a disinhibition of affect (Kinsella, Packer, & Olver, 1991; Lezak et al., 2004). A systematic review by Stéfan and Mathé (2016) found the prevalence of disruptive behaviors by excess including agitation to range from 11% to 70%, aggression from 25% to 39%, and irritability from 29% to 71% after TBI, whereas the prevalence of disruptive behaviors by default including apathy ranged from 20% to 71%. Individuals with TBI usually display multiple types or even apparently contradictory behaviors such as apathy and impulsivity, rather than a single behavior (Arnauld & Dromer, 2016). Behavioral and emotional dysregulation after TBI has been shown to be related to negative consequences on outcomes (e.g. Arnauld & Dromer, 2016; Wood, Liossi, & Wood, 2005).

1.1.7 NEUROPSYCHIATRIC DISORDERS AFTER TBI

TBI is associated with an increased relative risk of developing a range of psychiatric disorders (e.g. McAllister, 2013; Osborn, Mathias, & Fairweather-Schmidt, 2014), irrespective of injury severity (e.g. Perry et al., 2016). However, prevalence estimates of specific diagnoses vary substantially, likely because of methodological inconsistencies in studies (Mallya, Sutherland, Pongracic, Mainland, & Ornstein, 2015; Osborn et al., 2014). Overall, it remains controversial whether these disorders represent causation or association (Fuller, Ransom, Mandrekar, & Brown, 2016). Individuals with a preinjury history of psychiatric disorders appear more likely to develop neuropsychiatric disorders, although their nature may change after TBI, and novel psychiatric disorders can occur (Ponsford, Alway, & Gould, 2018). Presentation of psychiatric disorders in TBI can also be atypical, reflecting the deficits in cognition, behavior, and emotional functioning related to TBI (McAllister, 2013).

The most frequently reported secondary psychiatric changes to develop after TBI are depression and anxiety disorders (e.g. Perry et al., 2016; Ponsford et al., 2018). A meta-analysis of 99 studies (Osborn et al., 2014) found around 30% of TBI patients to be diagnosed with a major depressive disorder and around 40% to self-report clinically significant levels of depression. The prevalence rates of anxiety disorders after TBI are documented to range from 0.8% to 28% (Hioett & Labbate, 2002; Koponen et al., 2002; Moore, Terryberry-Spohr, & Hope, 2006; Stéfan & Mathé, 2016) and even up to 70% (Hibbard, Uysal, Kepler, Bogdany, & Silver, 1998). Posttraumatic stress disorder seems to be the most common (11–27%) anxiety disorder after TBI, followed by generalized anxiety disorder
(3–28%), obsessive-compulsive disorder (2–15%), and panic disorder (4–13%), with phobic disorders occurring less frequently (1–10%) (Bryant, Marosszeky, Crooks, Baguley, & Gurka, 2000; Hiott & Labbate, 2002; Koponen et al., 2002; Mallya et al., 2015; Moore et al., 2006). An association between the development of bipolar disorder and a prior TBI has also been shown in a meta-analysis (Perry et al., 2016). An increased risk of schizophrenia spectrum disorders following TBI was found in a large population-based study by Orlovská and colleagues (2014). Prevalence of psychosis after TBI is estimated at 0.7% (for review, see Stéfan & Mathé, 2016).

Neuropsychiatric syndromes following TBI have been found to negatively affect recovery (e.g. Osborn et al., 2014). Moreover, they contribute to functional impairments (Haagsma et al., 2015; Mallya et al., 2015) and deterioration in social functioning, activities of daily living (ADL) (Robinson & Jorge, 1994), and QoL (Haagsma et al., 2015; Osborn et al., 2014).

1.1.8 MOTOR PERFORMANCE DEFICITS IN TBI

The primary and secondary injuries of TBI will produce multiple impairments in motor performance of many patients. The major physical deficits that potentially contribute to mobility limitations, performing ADL, and participation in social, leisure, and work-related activities (Cifu et al., 1997; Duong et al., 2004) include balance problems (Englander et al., 1996; Geurts, Ribbers, Knoop, & van Limbeek, 1996; Lehman et al., 1990), muscle spasticity (Brashear & Elovic, 2016; Synnot et al., 2017), musculoskeletal deficits such as cervical spine injury and whiplash-associated disorders (Henrie & Elovic, 2016; Hartvigsen, Boyle, Cassidy, & Carroll, 2014; Magnusson, Karlberg, Mariconda, Bucalossi, & Dalmazzo, 2014), movement disorders or extrapyramidal disorders such as tremor, dystonia or posttraumatic parkinsonism (Barbosa, Casagrande, & de Andrade Freitas, 2018), muscle strength weaknesses (Williams, Morris, Schache, & McCrory, 2010), generalized nonspecific weakness (Henrie & Elovic, 2016), motor skill impairments (Rinne, Pasanen, Vartiainen, Lehto, Sarajuuri, & Alaranta, 2006), and motor coordination deficits (Rizzo et al., 2017). Although motor performance deficits have been found to be prevalent after moderate to severe TBI, the degree to which each influences mobility and other outcomes may vary substantially (Williams et al., 2013). Motor performance deficits assessed in Study II are addressed in the following sections.

Postural instability and balance problems are common following TBI and may persist for years (Hays et al., 2019) even in physically well-recovered patients (Rinne et al., 2006) and in patients with no obvious neurological
Paroxysmal positional vertigo is considered one of the most common causes of complaints of dizziness and imbalance post-TBI (Shepard et al., 2013). Balance problems are most evident in deep parenchymal or focal cerebral damages (Lehman et al., 1990). Injury to the central or peripheral vestibular system may result in considerable disability (Curthoys & Halmagyi, 2007).

The common neuropathology of TBI involving the prefrontal cortex commonly results to deficits in motor programming of voluntary movements such as delayed motor preparation (Russo, Incoccia, Formisano, Sabatini, & Zoccolotti, 2005), impaired predictive control and planning of movements, inability to program sequences of motor action in space and time, or impaired usage of feedback to correct errors (Caeyenberghs et al., 2010; Rizzo et al., 2017). Motor coordination deficits are common following TBI and long-term also in physically well-recovered patients (Rinne et al., 2006). In recent years, a number of studies have focused on deficits in visuomotor eye-hand coordination, the complex relationship between the visual and ocular motor systems, and the manual motor system resulting from TBI (Rizzo et al., 2017). Ocular motor deficits have been shown to occur in predictive control following TBI for moving targets and dynamic visuomotor tasks, highlighting difficulties in rapidly processing sensory information (Caeyenberghs et al., 2009 and 2010). Abundant evidence has suggested that eye movements and visuomotor skill of the upper limb are sensitive biomarkers for cerebral injury, especially when such biomarkers are combined synergistically (Heitger et al., 2004; Rizzo et al., 2017). Moreover, findings have highlighted the importance of interconnected functions of visual and manual motor systems in rehabilitation following TBI (Caeyenberghs et al., 2009).

Diverse and complex gait abnormalities are common after TBI (McFadyen, Swaine, Dumas, & Durand, 2003; Williams, Morris, Schache, & McCrory, 2009). Residual effects on walking may remain even though locomotor capacity is maintained in a highly functional person with TBI (McFadyen et al., 2003). Moreover, substantial evidence shows that many people with TBI experience difficulties with high-level motor skills such as running and jumping (Olver et al., 1996; Quinn & Sullivan, 2000; Williams et al., 2013). A marked proportion of TBI patients who can walk independently are unable to run (Ponsford et al., 1995; Hillier, Sharpe, & Metzer, 1997).
1.1.9 NEUROLOGICAL DISORDERS AND OTHER SEQUELAE OF TBI

The common neuropathology following TBI enhances the likelihood of additional neurological disorders and other symptoms in multiple forms. TBI represents an important modifiable risk factor for various medical conditions (e.g. Hammond & Malec, 2016), including such disorders as posttraumatic seizures (e.g. Annegers & Coan, 2000; Caballero et al., 2013; Ritter et al., 2016), disorders of the cranial nerves (e.g. Hammond & Masel, 2013), autonomic nervous system dysfunctions (e.g. Baguley & Nott, 2013), stroke (e.g. Burke, Stuc, Skolarus, Sears, & Zahuranec, 2013), sensory and sensory perceptual deficits (for recent reviews, see Callahan & Lim, 2018, Šarkić, Douglas, Simpson, 2019), pain disorders such as posttraumatic headaches (e.g. Hong et al., 2017; Stacey et al., 2017) and other bodily pain disorders (e.g. Cassidy et al., 2014), neuropathic pain (e.g. Widerström-Noga et al., 2016), central pain syndrome (e.g. Kim, Ahn, Cho, Kim, & Jang, 2015), and chronic pain (e.g. Tham et al., 2013), whiplash-associated disorders (e.g. Magnusson et al., 2014), neuroendocrine dysfunctions (e.g. Masel, 2013; Tudor & Thompson, 2018), gastrointestinal and nutritional problems (Kirby, Creasey, & Keely, 2013), metabolic dysregulation (e.g. Borsheim, Bui, & Wolfe, 2007), bone-related abnormalities (e.g. for recent review, see Bajwa, Kesavan, & Mohan, 2018), and multiple organ dysregulation (e.g. van Wessem & Leenem, 2018). Many of the risks associated with moderate to severe TBI have been suggested to be present also in milder injuries (Ishibe, Wlordarczyk, & Fulco, 2009).

The presence of these medical conditions and symptoms has been indicated to impair recovery (e.g. Horn et al., 2015; Masel, 2013), overall functional and psychosocial outcomes, well-being, and QoL, as well as to increase healthcare costs (e.g. Ciuffreda et al. 2016; Colucci, 2015; Dumke, 2017; Rao & Parko, 2015; Stacey et al., 2017; Sykora et al., 2017; Tudor & Thompson, 2018; Werff, 2016; Yablon & Towne, 2012) with diverse degrees of impact.

1.1.10 LIFE-LONG AND EVOLVING CONSEQUENCES FOLLOWING TBI

Evidence from multiple lines suggests that many patients with TBI experience ongoing long-term, lifelong, and also evolving symptoms over time, which impacts health, psychosocial outcomes, well-being, and QoL (Fadyl, Theadom, Channon, & McPherson, 2017; Hillbom, 1959b, 1965; Masel & DeWitt, 2010; Moretti et al., 2012; Ponsford, Downing, et al., 2014; Smith, et al., 2013; Wilson et al., 2017; for a recent meta-analysis, see Perry et al., 2016). TBI has been found to have lifelong effects on morbidity and increased risk for long-term mortality (e.g. Dams-O’Connor, Pretz, Billah, Hammond, & Harrison-Felix, 2015; Masel & DeWitt, 2010).
TBI may become a major risk factor with normal aging via acceleration of the ageing process and cognitive decline by reducing brain reserve (BR) capacities and neuroplasticity (Bigler, 2013; Corkin, Rosen, Sullivan, & Clegg, 1989; Moretti et al., 2012). A recent meta-analysis (Huang et al., 2018) revealed a significant association of prior TBI with subsequent dementia, but not with the development of subsequent neurodegeneration disease. Repetitive mTBIs have long been known to result in a much higher risk than a single TBI for late-life dementia (e.g. Lehman, Hein, Baron, & Gersic, 2012; Martland, 1928; McKee et al., 2013). A single TBI significantly increases the risk for a subsequent TBI with cumulative effects (Coronado et al., 2013).

Increased risk for long-term mortality following TBI has been identified across the age range, with predictors for both for mild (Dams-O’Connor, et al., 2015; McMillan, Weir, & Wainman-Lefley, 2014) and moderate to severe injuries (Haagsma et al., 2013; Harrison-Felix, Kolakowsky-Hayner, et al., 2012; Himanen et al., 2005; Masel & DeWitt, 2010; Wilson et al., 2017). Long-term mortality rates in TBI have remained relatively unchanged over the last 20 years (Brooks et al., 2013). TBI patients have been reported to be twice as likely to die as matched individuals (Harrison-Felix, Kolakowsky-Hayner, et al., 2012; Harrison-Felix, Kreider, et al., 2012). Life-expectancy is reported to be reduced by an average of six to seven years after TBI (Harrison-Felix, Kreider, et al., 2012; Ventura et al., 2010). Increased mortality has been found to be elevated for all cause-of-death categories, but especially for seizures, aspiration pneumonia, sepsis, accidental poisonings, and falls (Harrison-Felix, Kolakowsky-Hayner, et al., 2012). Comorbidities in TBI with life-shortening medical disorders have been suggested to be associated with increased mortality (Hammond & Malec, 2016). Meta-analyses (Bahraini, Simpson, Brenner, Hoffberg, & Schneider, 2013; Burke et al., 2018) have also consistently reported a heightened long-term risk of suicide for TBI patients across all severity levels. Moreover, functional disability, especially in cognitive and emotional functions, has shown to be a significant risk factor for long-term mortality in TBI (Brooks et al., 2013; Himanen et al., 2005; Neyens & Boyle, 2012; Unsworth & Mathias, 2017). Increased mortality has also been suggested to be secondary to the brain injury itself or to result from patient characteristics associated with the propensity for TBI (Fuller et al., 2016). Age, sex, and life-style factors have been shown to be related to long-term survival in TBI (e.g. Brooks et al., 2013; Fuller et al., 2016; Himanen et al., 2005).

Consistent evidence has emerged that many survivors in the chronic stage are living with under-recognized and poorly managed consequences of TBI, particularly those with mTBI (Kolakowsky-Hayner, 2012; Maas et al., 2017; Wilson et al., 2017). Thus, healthcare resources and long-term health management with proactive and rehabilitation interventions should be targeted to individuals suffering from TBI to improve their health and QoL (Harrison-
Felix, Kolakowsky-Hayner, et al., 2012; Goldstein & Diaz-Arrastia, 2018; Masel & DeWitt, 2010; Ventura et al., 2010; Wilson et al., 2017). Implementation of chronic health condition management has been suggested as an optimal way to address the lifelong care needed in TBI, to reduce the number of TBI individuals showing deterioration and delay decline, and to get TBI research the funding that it requires (Hammond & Malec, 2016; Levin et al., 1987; Masel & DeWitt, 2010; Wilson et al., 2017). A long-term survey on TBI outcomes (Brown et al., 2011) highlights the importance of providing more consistent follow-up with ongoing care, self-management education, and community-based services via proactive medical and psychosocial interventions to reduce premature deaths and enhance outcomes over the life span after TBI.

1.1.1 IMPACT OF TBI ON PSYCHOSOCIAL FUNCTIONING AND SUBJECTIVE WELL-BEING

Multifaceted cognitive, behavioral, emotional, and physical impairments have been documented in numerous studies to decrease psychosocial functioning among individuals with TBI. Common long-term psychosocial consequences following TBI reported widely by research include difficulties in establishing or maintaining relationships, social contacts, and family integration, sexuality and sexual functioning, a sense of belonging, recreation and leisure pursuits, achieving an education, involvement in productive life, and attaining adequate financial resources as well as challenges in the areas of independence and residence increasing dependency on family members and welfare systems (e.g. Andelic et al., 2018; Erler, Kew, & Juengst, 2019; Humphreys et al., 2013; Morton & Wehman, 1995; Oddy, Coughlan, Tyreman, & Jenkins, 1985; Shaikh, Kersten, Siegert, & Theadom, 2018; Stocchetti & Zanier, 2016; Thomsen, 1992; Whiteneck et al., 2016; Wood & Rutterford, 2006a). Overall, TBI commonly disrupts an individual’s ability to return to preinjury roles and routines.

Devastating deficits in cognitive, behavioral, emotional, and psychosocial functioning, in turn, result often in social isolation, loneliness, reduced self-esteem, impaired sense of body image, significantly impaired life satisfaction, and distress as well as increased stress and burden in family members (Caplan et al., 2016; Curvis, Simpson, & Hampson, 2016, 2018; Erler et al., 2019; Hoofien, Gilboa, Vakil, & Donovick, 2001; Pastore et al., 2015; Payne et al., 2018; Ponsford et al., 2014). Consequently, diverse deficits related to TBI have been found to have a profound impact on the QoL of the injured person as well as on his or her family and friends (e.g. Grauwmeijer et al., 2018; Maas et al., 2017; Manskow et al., 2017). Moreover, the interrelated nature of the areas of psychosocial functioning has been demonstrated (Williams, Rapport, Millis, & Hanks, 2014).
Along with therapeutic interventions for deficits in cognitive, behavioral, emotional, and physical functioning, psychosocial consequences need to be addressed in TBI rehabilitation (Ben-Yishay & Prigatano, 1990; Humphreys et al., 2013; Ponsford et al., 2014; Prigatano, 1999, 2005; Sohlberg & Mateer, 2017; Wilson, 2008). The importance of targeting interventions for psychosocial consequences has especially been recognized by those who have argued for the comprehensive-holistic neuropsychologically oriented rehabilitation approach to enhance psychosocial adjustment and overall outcome after TBI (e.g. Ben-Yishay et al., 1985; Christensen et al., 1992; Cicerone et al., 2008; Prigatano et al., 1984).

1.2 COMPREHENSIVE-HOLISTIC NEUROREHABILITATION APPROACH FOR TBI

1.2.1 MULTIPLE DOMAINS OF REHABILITATION AND INTERVENTION TARGETS AFTER TBI

TBI has been considered to be one of the most challenging areas in rehabilitation medicine (Borg et al., 2011; Cnossen et al., 2017). The complexity is due to the nature of TBI as a heterogeneous and lifelong disorder with a myriad of consequences and changing needs over time, impacting multiple aspects of daily functioning, relationships, community integration, and QoL (CDC, 2017; Corrigan et al., 2013; Katz et al., 2013; Maas et al., 2017). The cumulative impact of deficits on daily living is apparent considering that most tasks require the integration of many cognitive, behavioral, emotional, and physical abilities (Dams-O’Connor & Gordon, 2013). TBI in younger people often disrupts achievement of important life cycles, whereas in older people TBI presents specific problems related to aging (Katz et al., 2013; Levine & Flanagan, 2013). Consequently, the rehabilitation needs and targets after TBI are numerous, including cognitive, emotional, behavioral, physical, personal, and environmental domains (WHO, 2001; Maas et al., 2017).

Factors impacting rehabilitation after TBI. Individual characteristics such as premorbid functioning and personality, nature and severity of TBI, levels of social support and environmental demands impact TBI rehabilitation (Sohlberg & Mateer, 2017; Turner-Stokes, Disler, Nair, & Wade, 2005; Zasler et al., 2013). Moreover, different forms of rehabilitation interventions are appropriate for different subgroups of TBI patients and at different phases after the injury to optimize outcomes (CDC, 2017; Maas et al., 2017; Zasler et al., 2013). Although the optimal timing for rehabilitation is debated, results suggest that better functional outcome occurs in patients who have received early onset and continuous comprehensive rehabilitation (Andelic, Bautz-Holter, et al., 2012;
Andelic, Tornas, et al., 2014; Borg et al., 2011). Furthermore, evidence supports that functional improvement or deterioration after TBI can occur for many years (Corrigan & Hammond, 2013; Green, 2015). Acknowledging the long-term consequences of TBI is critical to permit proper allocation of rehabilitation interventions and to intervene the risk factors for poor outcome (Maas et al., 2017; Wilson et al., 2017). TBI patients’ level of functional recovery and independence, geographic factors, and financial resources also impact the type of rehabilitation care available (CDC, 2015). Although rehabilitation treatments and goals for TBI patients are typically designed to enhance and maintain independence in ADL, social participation, community integration, and QoL, it is essential that they are personalized in regard to patient characteristics and injury, preinjury functioning, and individual goals to maximize the potential for well-being (CDC, 2015; Cicerone et al., 2008; Maas et al., 2017; Savulich, Menon, Stamatakis, Pickard, & Sahakian, 2018).

Over the last three decades, standards of care, rehabilitation interventions and research for TBI patients have developed, yet robust evidence for effective practices are scarce and evidence-based guidelines do not exist for most rehabilitation interventions (Borg et al., 2011; Fronter et al., 2017; Maas et al., 2017; Malec, 2013; Ottenbacher, Jette, Fuhrer, Granger, 2012). In addition, recommended practices are inconsistently implemented between centers and often do not sufficiently address to the diversity of consequences related to TBI (Cnossen et al., 2017; Maas et al., 2017). Wide variations have also been found in structure and process characteristics of TBI rehabilitation (Checkley et al., 2014; Cnossen et al., 2017).

It is well-recognized that systems of care should acknowledge these varying needs with theoretically sound and cost-effective rehabilitation models to promote recovery, reduce disability, and improve health, functioning, independence, social reintegration, and QoL and also to address the long-term complications of people with TBI (Coetzer, Roberts, Turnbull, & Vaughan, 2018; Maas et al., 2017; Ottenbacher et al., 2012). However, the actions for TBI rehabilitation have lagged in the healthcare system, research, and society (Borg et al., 2011; Coetzer, 2018; Malec, 2013). Although the number of people living with TBI is increasing (GBD, 2015), rehabilitation services have remained underdeveloped, insufficiently resourced, and poorly valued (Krug & Cieza, 2017), especially with regard to postacute, long-term community-based rehabilitation and support services (Coetzer et al., 2018). Calls for action to strengthen rehabilitation services and research have recently been issued by WHO (2017) and the NIH Center for Medical Rehabilitation Research, the agenda of which stresses the need for understanding the lifelong consequences and burden of TBI (Frontera et al., 2017).
**Multiprofessional teamwork for TBI rehabilitation.** Considering the marked diversity, complexity, and interaction of consequences after TBI it is evident that persons with TBI require comprehensive rehabilitation with multiple healthcare professionals and is best addressed by multidisciplinary and interdisciplinary team approaches (Maas et al., 2017; Körner, 2010; Turner-Stokes, 2008; Wertheimer et al., 2008). Disciplines typically involved in TBI rehabilitation include physicians specialized in neurology and/or rehabilitation, neuropsychologists, nurses, physiotherapists, occupational therapists, speech and language pathologists, and social workers.

Benefits of coordinated multiprofessional teamwork in neurorehabilitation have been shown for patients, team members, the team, and the service (e.g. Pagan et al., 2016). Multiprofessional approaches have also been demonstrated to be both clinically and economically cost-effective (Turner-Stokes, 2008). Consistently better results in the teamwork process have been attained by teams using with the interdisciplinary approach, with a high degree of collaboration between team members in setting rehabilitation goals and carrying out rehabilitation plans (Bakheit, 1996; Körner, 2010; Rothberg, 1981).

**Factors impacting TBI rehabilitation research.** Research on TBI rehabilitation has been shown to be difficult, addressing methodological challenges and obstacles that do not occur in typical clinical drug trials (Frontera et al., 2017; Maas et al., 2017; NIH, 1999). Adequate sample sizes, appropriate comparison groups, and viable control conditions are seldom achieved in clinical rehabilitation settings. Other important considerations that impose challenges for TBI rehabilitation research include the marked heterogeneity of patients, interventions, and settings, repeatability certitude, dosing, possible confounders of intervention effect, timescale over which rehabilitation may have an effect, and precision of outcome metrics (Frontera et al., 2017; Turner-Stokes, 2008). Ethical aspects concern the cognitive capacity of TBI patients to give informed consent to participate in research and the randomization of patients to no treatment or standard care (Turner-Stokes, 2008).

### 1.2.2 COMPREHENSIVE-HOLISTIC REHABILITATION PROGRAMS (CHRPs)

**Development of CHRPs.** In the history of the comprehensive-holistic neuropsychologically oriented rehabilitation approach, Kurt Goldstein (1942, 1952, 1959) is considered the eminent pioneer. While working with soldiers with TBI during World War I, he built up a renowned clinic in Germany. He acknowledged that TBI patients need environments that help them to avoid...
catastrophic reactions, i.e. behavioral manifestation of the injured person’s experience of failure to cope in particular situations, reflected as severe anxiety (Goldstein, 1942, 1959). Within such an environment, it could be possible to engage optimally in rehabilitation, which gradually would result in the individual finding a new meaning to life after TBI.

Yehuda Ben-Yishay incorporated many of Goldstein’s ideas and developed a milieu rehabilitation program, the New York University Head Trauma Program which has been in existence since 1978. Prior to this he had the opportunity to translate the idea of holistic rehabilitation into practice with Israeli soldiers with TBI in the early 1970s (Ben-Yishay, 1996). In this day program, patients undergo intensive, systematic, and well-coordinated therapeutic interventions designed to restore their ability to function and to help them to deal with intrapersonal and interpersonal difficulties (Ben-Yishay, Rattok, Lakin, Piasetsky, Ross, Silver, Zide & Ezrachi, 1985; Diller, 1987). The emerging role of psychotherapy interventions for TBI patients was characteristic of the Neuropsychological Rehabilitation Program, which George Prigatano established in 1980 in Oklahoma and in 1986 in Phoenix (Prigatano, Fordyce, Zeiner, Roueche, Pepping & Wood, 1984). Inspired by these developments, similar CHRPs were established in Europe including Denmark (Christensen & Teasdale, 1995), Finland (Kaipio, Sarajuuri, & Koskinen, 2000), the United Kingdom (Wilson, Evans, Bretnall, Bremner, Keohane, & Williams, 2000), Germany (Kühne, 2009), and the Netherlands (van Balen, Jorritsma, Groet, & Vink, 2002). This thesis evaluates the outcomes of the Finnish CHRP, the Individualized Neuropsychological Subgroup Rehabilitation Program (INSURE), describing its structure and content in the methods section of Study I.

The main elements of CHRPs include the promotion of a therapeutic setting; neuropsychological rehabilitation including psychotherapeutic interventions and cognitive training; vocational guidance and support (e.g. protected work trials and placements); family education and therapeutic support; appropriate management of affective reactions in interdisciplinary rehabilitation teams; and follow-up care (Ben-Yishay et al., 1985; Cicerone et al., 2008; Kaipio et al., 2000; Koskinen & Sarajuuri, 2002a; Prigatano, 1999; Sarajuuri & Koskinen, 2006). The CHRPs are provided within a setting of an organized and supportive therapeutic milieu (Ben-Yishay, 1996), including mutual collaboration of peer patients, their families and/or significant others, and members of a multidisciplinary staff with a steady leadership.

Therapies and interventions are implemented in both intensive individual and group formats in a coordinated fashion to facilitate each other. Attention is directed to establishing a good therapeutic relationship to accomplish optimal
psychosocial adjustment through improved awareness and acceptance. The goal of CHRP is reestablishment of meaningful life in the face of the persisting limitations imposed by TBI.

The effectiveness of postacute CHRPs in enhancing psychosocial adjustment and outcome, reducing emotional stress, and increasing self-esteem has been supported by evidence from two randomized controlled trials (Cicerone et al., 2008; Ruff & Niemann, 1990), a few non-randomized comparative trials (Cicerone et al., 2004; Fryer & Haffey 1987; Goranson et al., 2003; Hashimoto, Okamoto, Watanabe, & Ohashi, 2006; Parente & Stapleton, 1999; Rattok et al., 1992; Svendsen & Teasdale, 2006), and several cohort studies without concurrent controls (Ben-Yishay et al., 1985, 1987; Christensen et al., 1992; High et al., 2006; Klonoff et al., 1998, 2007; Laatsch & Stress, 2000; Malec, 2001; Nienmeier et al., 2005; Perumparaichallaia, Lewina, & Klonoff, 2020; Prigatano et al., 1984, 1994; Sander et al., 2001; Schonberger et al., 2006; Seale et al., 2002; Svendsen et al., 2004). Overall, controlled studies evaluating psychosocial outcomes of the CHRP in chronic TBI have been scarce, likely due to the several methodological challenges involved. In this thesis, these topics are addressed in Study I.

1.2.3 NEUROPSYCHOLOGICAL REHABILITATION AS AN INTRINSIC COMPONENT OF CHRPs

Neuropsychological rehabilitation (NR) is an intrinsic component of CHRPs. Interventions emphasize metacognition and emotional regulation for cognitive and emotional difficulties, interpersonal behaviors, and psychosocial functioning. Improvements in everyday functioning are assumed to be attained through effective application of residual cognitive skills and compensatory strategies to cope with deficits, rather than remediation of them per se. Evidence indicates that NR is beneficial for both acute and postacute TBI patients, even during the later postacute community care stages (e.g. Andelic et al., 2012; Cicerone et al., 2011; Maas et al., 2017; Malec & Basford, 1996; Rohling, Beverly, Faust, & Demakis, 2009; Turner-Stokes, 2008).

Findings have highlighted the complex interplay after TBI among cognitive, emotional, and behavioral deficits and their inevitable psychosocial consequences (Bechara, Damasio, & Damasio, 2000; Beer, John, Scabini, & Knight, 2006; Consensus Conference JAMA 1999; Ponsford, Dowling, et al., 2014; Sohlberg & Mateer, 2017; Sbordone, 2000; Wilson, 2008). Yet recognized by the pioneers of the CHRP approach, NR should address all of these aspects of human functioning with appropriate therapeutic interventions to ameliorate them, while increasing awareness and understanding of a new self to alleviate disability.
Introduction and handicapping conditions (Cicerone et al., 2008; Diller, 2005; Prigatano, 1999; Wilson, 2008). Moreover, rehabilitation should encompass personally meaningful topics, activities, settings, and interplays (Ben Yishay & Prigatano, 1990; Sohlberg & Mateer, 2017; Wilson, 2008; Ylvisaker & Feeny, 2000). According to Prigatano (2000) NR should primarily attend to patients’ personal experiences and help them to adjust to their deficits in the context of interpersonal situations. The focus of NR is to establish a meaningful and satisfactory life and to improve well-being for people with TBI (Cicerone et al., 2008; Evans, 2012).

Cognitive aspects of neuropsychological rehabilitation. Cognitive rehabilitation is today a standard component of TBI medical care (e.g. Cicerone et al., 2011; Rohling et al., 2009; Wilson, 2008) with evidence-based guidelines (Bayley et al., 2014). Broad evidence from reviews (e.g. Cicerone et al., 2000, 2005, 2009, 2011, 2019; Rees et al., 2007) and meta-analyses (Kennedy et al., 2008; Rohling et al., 2009) has demonstrated that TBI patients benefit from cognitive rehabilitation for disabilities of attention, memory, executive function, and social communication skills.

Cognitive rehabilitation interventions may have various approaches, including (1) reinforcing previously learned basic cognitive skills and residual abilities by training; (2) promoting compensatory strategies through metacognitive training and guiding principles that can be generalized across diverse contexts; (3) establishing external compensatory mechanisms such as using technological aids or cognitive orthotics, environmental modifications, and support; and (4) enabling persons to adapt to their cognitive disability by increasing awareness and acceptance of their condition. Interventions should be tailored to each person's needs and are often combined to improve functioning relevant to their everyday lives (Cicerone et al., 2000; Dams-O’Connor & Gordon, 2013; Maas et al., 2017; Tsaousides & Gordon, 2009; Wilson 2008).

Emotional aspects of neuropsychological rehabilitation. The importance of management of emotional reactions to impairments has become progressively clearer to make rehabilitation more complete and to improve long-term psychosocial outcomes after TBI (e.g. Ben-Yishay, 1978; Cicerone, 1991; Coetzer, 2015; Goldstein, 1942, 1959; Hillbom, 1961a, 1961b; Judd, 1999; Kaipio et al., 2000; Klonoff, 2010; Koskinen, & Sarajuuri, 2013; Laaksonen & Ranta, 2013; Prigatano, 1999; Ruff & Chester, 2014). Dealing with the emotional and personal adjustment issues of persons with TBI is likely to make the difference between successful and unsuccessful outcome of rehabilitation (Prigatano, 1999; Wilson, 2008). Recently, evidence for the effectiveness of psychotherapy in the brain-
injured population overall has started to be reported (e.g. Doering & Exner, 2011; Hofer, Holtforth, Frischknect, & Znoi, 2010).

Development of psychotherapeutic interventions has been greatly assisted by the work of Ben-Yishay with colleagues (1978) and Prigatano with colleagues (1986) who applied Goldstein’s (1942, 1952, 1959) insights to their CHRPs. More recent developments have drawn from the broad field of existing theories of psychological therapies, including psychoanalytic approaches (e.g. Kaplan-Solms & Solms, 2000), cognitive therapy (e.g. Gracey & Onsworth, 2008; Manchester & Wood, 2001), psychodynamic approaches (e.g. Klonoff, 2010), acceptance and commitment therapy (e.g. Kangas & McDonald, 2011), and mindfulness-based approaches (Bédard et al., 2014; Johansson, Bjuhr, & Rönnbäck, 2012) as well as generic models (e.g. Coetzer, 2007) and integrated approaches (e.g. Judd, 1999; Ruff & Chester, 2014), such as neuropsychotherapy (Laaksonen & Ranta, 2013), among many models adapted for application within brain-injured persons. Regardless of the therapy approach, psychotherapy in the context of TBI requires understanding of the phenomenon of TBI, neuropsychological and psychological consequences related to TBI, and psychodynamic factors (Gainotti 1993; Moser, 1999). The goals of psychotherapy after brain injury could be summarized as: (1) to help patients to achieve a better understanding of one’s self and one’s behavior, (2) to achieve a renewed sense of identity, (3) to learn to behave in one’s own best interest by making appropriate choices to attain an optimal psychosocial adjustment, (4) to cope and to make a personal adjustment to the reality of one’s life, (5) to foster a sense of realistic hope, and (6) to re-establish a sense of meaning in life (Ben-Yishay et al., 1978; Cicerone, 1989; Coetzer, 2015; Goldstein, 1942; Klonoff, 2010; Laaksonen & Ranta, 2013; Prigatano et al., 1999).

TBI rehabilitation proceeds by helping patients through the phases of increased awareness, acceptance and realism about the consequences of brain injury in life, setting of attainable goals, and use of new insights, skills, and compensations (Klonoff, 2010). Psychotherapeutic interventions are often required to facilitate these processes (Coetzer, 2015). The process of identity reconstruction is an essential element in longer term adjustment (e.g. Biderman, Daniels-Zide, Reyes; & Marks, 2006; Gracey & Ownsworth, 2008). In this respect, therapists should build up a thorough understanding of patients’ background history, including development, personality attributes, psychodynamics, and aspirations (Coetzer, 2015; Klonoff, 2010). Prigatano (e.g. 1999) emphasized therapists’ need to enter patients’ phenomenological field, that is, to have a clinical psychological attitude towards patients’ personal experiences, to help them better understand their personal reactions to the consequences of TBI, and to facilitate the adjustment process.
The process to begin to deal with emotional reactions, changes, personal losses, mental confusion, and frustration produced by TBI requires on the patient’s part courage and commitment with reduced cognitive resources to progressively face the realities in their life (Prigatano, 1999). According to Prigatano (1999), focusing on issues related to the primary human symbols of normality, i.e. work, love, and play, which provide meaning to many people’s lives, can be helpful in guiding the psychotherapeutic process. The ability to work, love and play helps individuals to cope with suffering and loss after brain injury, to achieve normality and a sense of wholeness, and to re-establish personal identity and a psychological sense of meaning in life (Coetzer, 2015; Prigatano, 1999). The symbol of work is the experience of being productive and useful, which is important for psychological well-being (Hall & Lindzey 1978). The symbol of love is related to the ability to maintain meaningful interpersonal relationships, enabling psychological relatedness and experiencing not being alone psychologically (Prigatano, 1999). Overall, the issues of love and work have been of central importance to the most influential theories of psychological well-being (e.g. Erikson 1963; Rogers, 1961). Besides work and love, the Jungian (Jung & von Franz, 1964) concept of play greatly contributes to a psychological sense of meaning in a person’s life (Prigatano, 1999). It reflects our capacity to indulge playful thoughts, actions, and feelings, and to deal with the inner world of self (Prigatano, 1999). Guidance to make good choices concerning work, love, and play aligned with the patient’s impairments is relevant in NR.

Besides individual therapies, group rehabilitation can be a valuable component of NR after TBI (Cicerone, 1989; Klonoff, 2010; Prigatano et al., 1986). Group therapies offer placement of the patients in a social situation that can serve to reduce their social isolation. Group therapies can provide opportunities for patients to hear and share experiences with peers and mentors to alleviate the sense of alienation and to improve insight and acceptance. Moreover, the group process facilitates acquisition of hope, altruism, socialization, learning of social skills, coping techniques, and psychological adjustment (Delmonico, Hanley-Peterson, & Englander, 1998; Klonoff, 2010; Langenbahn, Sherr, Simon, & Hanig, 1999; Prigatano et al., 1986).

Broad evidence of reviews (Ardito & Rabellino, 2011) and meta-analyses (Horvath & Luborsky,1993; Horvath & Symonds, 1991; Karver, Handelsman, Fields, & Bickman, 2006; Martin, Garske, & Davis, 2000; Shirk & Karver, 2003) suggest that the quality of the therapeutic relationship or alliance in the therapeutic process is the most robust factor associated with successful outcome across all psychotherapy approaches and outcome measures. Clinical outcomes have validated a therapeutic relationship that is open to empathic, emotional, and affective influences as an essential factor and vehicle for transformative
processes in psychotherapy (Onnis, 2016). Likewise, in CHRPs a good working alliance has proven predictive for a reduction in patients’ depressive symptoms (Schönberger, Humle, & Teasdale, 2006a), improved awareness (Schönberger, Humle, & Teasdale, 2006b) and employment status (Klonoff et al., 2001; Prigatano et al., 1994; Schönberger, Humle, Zeeman, & Teasdale, 2006).

Supported by current neuroscientific research, neural plasticity, growth, and integration are promoted in psychotherapy (Cozolino, 2014). Psychotherapy has been demonstrated to have the potential to modify dysfunctional neural networks associated with affective disorders in functional neuroimaging studies (e.g. Goldapple et al., 2004; Peres & Nasello, 2008; Roffman, Marci, Glick, Dougherty, & Rauch, 2005; Wessa, Jatzko, & Flor, 2006). Subjective experiences, such as perceptions, memories, and belief systems brought forth in the psychotherapeutic process (Peres & Nasello, 2008) have been shown to be able to alter the flow of neural information (e.g. Kraemer, Macrae, Green, & Kelley, 2005). Moreover, interpersonal relations, especially the nature of interactions, have been demonstrated to shape the neural architecture of our brain (e.g. Cozolino, 2014).

1.2.4 ASSOCIATION OF COGNITIVE AND MOTOR PERFORMANCE IN TBI RELATED TO NEUROREHABILITATION

Cognitive abilities influence and are influenced by emotional and behavioral deficits as well as by diverse physical impairments (Liotti & Mayberg, 2001; NIH, 1999; Sarter, Gehring, & Kozak, 2006). Cognitive and motor functions have usually been studied as distinct domains in isolation or in dual-task performance research protocols involving simultaneous cognitive tasks and motor tasks, particularly walking (McFadyen et al., 2017; Sosnoff et al., 2008). However, emerging observations have provided evidence that neural networks related to cognitive functions may also be recruited during motor tasks (McCulloch, Buxton, Hackney, & Lowers, 2010; Montero & Hachinski, 2014; Serrien, Ivry, & Swinnen, 2007; Sosnoff et al., 2008). The fact that walking is a cognition-based action has been noted from findings that cognitive impairments resulting from different neurological disorders likely influence balance, postural control, and gait (e.g. Alexander & Hausdorff, 2008; Giordano & Persad, 2005). The convergence between motor functions and cognition and the generic brain areas between the interconnection of these domains have been shown to become particularly apparent when exploring complex motor tasks involving sequencing or coordination (Serrien et al., 2007). Overlap between movement organization and cognition is obvious in frontal lobe areas linked to response selection,
decision-making, and monitoring of complex tasks (Picard & Strick, 1996). Fronto-striatal networks (Alexander, DeLong, & Strick, 1986) connecting frontal lobe regions with basal ganglia that mediate motor, cognitive, and behavioral functions have been suggested to be especially important for functions involved in the control of complex actions (Chudasama & Robbins, 2006). Depending on task demands, also the rostral part of the dorsal premotor cortex and precuneus and, the posteromedial part of the parietal lobe will become recruited during movement organization (Cavanna & Trimble, 2006; Picard & Strick, 2001). Prefrontal areas participate in complex motor tasks to execute cognitive control through attentional processes (Rowe, Friston, Frackowiak, & Passingham, 2002) that interrelate with other networks (Posner & Petersen, 1990) or that are directly connected to reserved sensorimotor regions (Eimer, Van Velzen, Gherri, & Press, 2006). Involved neural resources have been assumed to depend on the task complexity shown by neuroimaging data with increased connectivity patterns (Rissman, Gazzaley, & D’Esposito, 2004). Thus, the more complex a motor task is, the more prone it is to the impact of cognitive abilities (Brown & Marsden, 1991). Cognitive control becomes most evident when irregular, erroneous, or ambiguous stimuli are presented during movement organization towards the initial motor intention (Fink et al., 1999; Serrien et al., 2007).

Impairments of skilled movements are typically incurred following damages to the prefrontal (Luria, 1973), premotor (Freund & Hummelsheim, 1985), and parietal regions (Serrien, Nirkko, & Wiesendanger, 2001), as in subcortical areas such as the cerebellum (Serrien & Wiesendanger, 2000) and basal ganglia (Agostino, Berardelli, Formica, Accornero, & Manfredi, 1992). Compensatory activation related to neuropathology usually induces either increased activation in areas supporting motor- and/or sensory-guided control, such as premotor and parietal regions and the cerebellum (Samuel et al., 1997), or increased activation in frontal regions related to reinforced cognitive activity (Wu & Hallett, 2005). The neural mechanisms underlying cognitive control of skilled motor tasks are suggested to emerge in a similar way across functional domains, with enrollment of a larger network when the need for monitoring increases (Ivry, Diedrichsen, Spencer, Hazeltine, & Semjen, 2004; Serrien & Ivry, 2007; Shallice & Burgess, 1996).

Meta-analyses (Patel, Spreng, & Turner, 2013) have provided evidence for links between motor and cognitive brain regions through neuroimaging and neuroanatomical studies showing co-activation of these regions during the performance of motor or cognitive tasks. In one of the few studies to explore relationships between cognitive and motor performance in TBI, Geurts and colleagues (1999) examined whether balance was associated with mental functioning after mTBI with persistent cognitive and postural control symptoms.
Their results indicated a possible association between balance and cognitive performance, specifically mental speed and working memory (Geurts, Knoop, & van Limbeek, 1999). Likewise, Sosnoff and colleagues (2008) found a significant association between motor and cognitive functioning after mTBI, showing links between mental processing time, working memory, and balance impairments. This association was not found prior to injury, suggesting a novel contribution of this study that neural insults result in an increased cognitive-motor association (Sosnoff et al., 2008). Cantin and colleagues (2007) reported that measures of executive functioning and attention may be associated with locomotor activities in complex environments after moderate to severe TBI, but not in healthy participants. The slowed processing and motor reaction times, frequently seen after TBI have been suggested to be due to lowered cortical connectivity across brain regions as a common injury mechanism that underlies impairments in balance, coordination, and cognitive processing, among others (Ghalar & Ivry, 2008; McNamara et al., 2007, Walker & Pickett, 2007). Overall, there is currently a shortage of research examining the association between cognition and motor functions (Rosenbaum, 2005; Sosnoff, 2008), particularly in patients with TBI, which is the focus of Study II.

The acknowledged benefits of physical conditioning and exercise for people with TBI have been reported to include improved sleep patterns, reduced fatigue, stronger endurance, increased self-confidence, and improved individual autonomy (Jankowski & Sullivan, 1990; Sullivan, Richer, & Laurent, 1990). In addition to direct physical and physiological benefits, motor exercise has been shown to contribute to maintaining cognitive function and to have positive effects on cognitive information processing, memory, and neurobehavioral deficits in several populations (Baker et al., 2010; Colcombe & Kramer, 2003; Fordyce & Farrar, 1991; Spirudo & Asplund, 1995; Tanaka et al., 2009), including chronic TBI (Grealy, Johnson, & Rushton, 1999). Collectively, these findings related to the association between cognition and motor functions in TBI may potentially have important clinical implications in the field of neurorehabilitation. This topic is discussed in Study II.

1.2.5 HEALTH ECONOMICS AND COST-EFFECTIVENESS OF REHABILITATION FOR TBI

TBI is a critical public health and socioeconomic problem throughout the world. The estimated TBI-related costs in Europe for 2010 exceeded 33 billion euros, of which direct costs accounted for 41% and indirect costs 59% (Gustavsson et al., 2011; Olesen et al., 2012). In the United States, the economic burden, was
reported to be about 220 billion US dollars in 2009 (Orman et al., 2011). About 30% of these costs constituted productivity losses and about 60% intangible costs such as lost QoL (Orman, Kraus, & Zaloshnja, 2011). The global annual TBI-related cost has extrapolated to exceed 400 billion US dollars (Maas et al., 2017), which represents about 0.5% of the annual gross world product (The World Bank, 2017). mTBIs are estimated to account for over a quarter of this sum (Thurman, 2001).

A review by Humphreys and colleagues (2013) showed that very little research has been published on the economic burden that patients with TBI pose on families, careers, and society as a whole. Data from 16 European countries (Majdan et al., 2017) on the public health consequences of TBI deaths showed nearly 375,000 years of life lost (YLL) in 2013, which translates to about 259 TBI-related YLLs per 100,000 people per year and to about 24.3 YLLs per TBI death. Almost 74% of all the YLL due to TBI were incurred by age groups with the potential to work (Majdan et al., 2017). Globally, the burden of TBI was estimated to result in 8.1 million years lost with disability in 2016 (GBD, 2019).

There is increasingly strong evidence for the cost-effectiveness of TBI rehabilitation and for the notion that the additional investment in rehabilitation is offset relatively quickly by long-term savings in costs of care (Turner-Stokes, 2007; Turner-Stokes, Williams, Bill, Bassett, & Sephton, 2016). Potential cost savings through successful TBI rehabilitation programs have been reported to be substantial, although current research is subject to differing methodological approaches in terms of costs and outcomes (Humphreys et al., 2013). Alongside significant clinical and psychosocial outcomes, cost-efficacy of TBI rehabilitation has been demonstrated for early specialist inpatient multidisciplinary rehabilitation (Cooney & Carroll, 2016; Duarte et al., 2018; Turner-Stokes et al., 2016; Yè, 2013), integrated interdisciplinary program of seamless care from acute hospital to discharge to patient’s homes, rehabilitation institutions or long-term care facilities (Khan, Khan, & Feyz, 2002), supported employment services (Wehman et al., 2003) and postacute community-based comprehensive integrated rehabilitation (Turner-Stokes, 2004), and neurobehavioral rehabilitation programs regardless of time since injury (e.g. Wood, McCrea, Wood, & Merriman, 1999; Worthington et al., 2006). However, with fairly lengthy intervention periods (~ 6 months), the cost of the CHRPs has constituted a major critique of these interventions (Wilson, 1997). This topic is discussed in Study I.
1.3 OUTCOMES FOLLOWING TBI

1.3.1 MULTIDIMENSIONAL OUTCOME ASSESSMENT

Diverse adverse and long-term consequences of TBI generate difficulties to return to many avenues of premorbid life affecting multiple outcome domains (CDC, 2017; Ponsford et al., 2014; Zasler et al., 2013). This often leads to markedly reduced well-being and QoL of the person injured and impacts his or her family and friends, also imposing a substantial economic burden on the community and society in general (Aertker et al., 2016; CDC, 2017; Maas et al., 2017).

It is increasingly evident that outcome assessment of TBI should be multidimensional to show treatment effects or to serve as endpoints for clinical studies (Kean & Malec, 2014; Maas et al., 2017; Wilde et al., 2010). Numerous measures, including crucial outcome domains such as neuropsychological deficits, psychological health, and health-related QoL (HRQoL) (Coons, Rao, Keininger, & Hays, 2000), should be applied (Maas et al., 2017; Polinder, Haagsma, van Klaveren, Steyerberg, & van Beeck, 2015). However, this has not been done in most TBI outcome studies (Humphreys et al., 2013), rather outcome has been measured with gross global tools, such as the Glasgow Outcome Scale (GOS) (Jennett, Snoek, Bond, & Brooks, 1981), or by measuring a single outcome domain. Figure 1 depicts a recent conceptual model of multidimensional outcome assessment for TBI generated by The Lancet Neurology Commission (Maas et al., 2017). Although, the use of composite instruments for measuring TBI outcome is called for to guide better clinical management (Bagiella et al., 2010, Kean & Malec, 2014; Maas et al., 2017), it is important to have the option to select from appropriate validated instruments to examine specific clinical or research issues (McMillan, Bigler, Teasdale, Ponsford, & Murray, 2018). In this thesis, outcome assessment after TBI rehabilitation was addressed in Studies I and III.
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Figure 1. Multidimensional outcome assessment of TBI domains of outcome assessment included in Common Data Elements for TBI (NIH) with respective example measures in parentheses. Outcome is defined by selecting domains of interest and choosing measures that reflect each domain. Abbreviations: CRS-R, Coma Recovery Scale, Revised; GOS, Glasgow Outcome Scale; GOSE, Extended GOS; QOLIBRI, Quality of Life after Brain Injury Scale; QOLIBRI-OS, QOLIBRI Overall Scale; RPQ, Rivermead Post-Concussion Symptom Questionnaire; SF-36, 36-Item Short Form Health Survey. Adapted from Maas and colleagues (2017) by permission of Elsevier.

1.3.2 FACTORS INFLUENCING OUTCOME

Multiple factors are related to outcome after TBI which makes outcome prediction complicated (e.g. McMillan et al., 2018; Schönberger, Ponsford, Olver, Ponsford, & Wirtz, 2011). Some factors emerge only indirectly when their effect is mediated by other factors (Schönberger et al., 2011), and some play a greater role in the early or later stages of recovery (Brown et al., 2005; Wood & Rutterford, 2006b). Factors influencing TBI outcome comprise a complex interplay between various premorbid characteristics, injury-related factors, postinjury impairments, and environmental factors (Bush et al., 2003; Holland & Schmidt., 2015; Humphreys et al., 2013; McMillan et al., 2018; Novack et al., 2001; Ponsford et al., 2016; Rassovsky et al., 2015; Santarsieri et al., 2015; Schönberger et al., 2011; Sela-Kaufman et al., 2013; van Velzen et al., 2009). An overview of the factors contributing to outcome after TBI is given in the following section.

Among premorbid factors, age, particularly age over 50 years at the time of injury (Senathithi-Raja, Ponsford, & Schonberger, 2009, 2010), has been strongly linked to poorer outcomes (e.g. Holland & Schmidt, 2015; Novack et al., 2010; Ponsford et al., 2014; Schönberger et al., 2011). On the other hand, individuals having TBI during childhood or adolescence might have poor employment outcomes while still struggling to complete their education (Wehman, Targett,
& Avellone, 2017). Gender has also been found to affect TBI recovery and outcome in numerous studies (e.g. Holland & Schmidt, 2015). Most of the evidence suggests an improved recovery and better outcomes for females than for males following TBI (Niemeyer, Marwitz, Lesher, Walker, & Bushnik, 2007; Ratcliff, 2003; Saban, Smith, Collins, & Pape, 2011). Investigations of mechanisms behind this effect have mostly focused on progesterone as a protective factor (Holland & Schmidt, 2015; Sarkaki, Haddad, Soltani, Shahrokhi, & Mahmoodi, 2013).

Preinjury cognitive functioning, higher education, and employment status have mostly been shown to be significant predictors of employment outcome after TBI (Donker-Cool, Wind, & Frings-Dresen, 2016; Ownsworth & McKenna, 2004; Schönberger et al., 2011), but not in all studies (van der Naalt et al., 1999). Leisure activity has been demonstrated to predict cognitive, emotional, and daily functioning besides employment after TBI (Rassovsky et al., 2015). Preinjury psychiatric and mood disorders have been found to be related to postinjury employment directly (Whelan-Goodinson et al., 2008) or by their association with emotional, cognitive and behavioral impairments (e.g. Schönberger, 2011). Reviews on the effect of preinjury substance abuse on TBI outcome (Corrigan, 1995; Parry-Jones, Vaughan; & Cox, 2006; Willemse-van Son et al., 2007) have been mixed, but mainly revealing poorer outcomes (for recent meta-analysis, see Unsworth & Mathias, 2017). Premorbid personality characteristics including personality traits, attachment style, and temperament, have long been recognized to play an important role in variability in outcomes after TBI (Luria, 1948/1963; Prigatano, 1999; Rush, Malec, Brown, & Moessner, 2006) and to robustly moderate the effect of TBI severity on employment outcome (Sela-Kaufman et al., 2013). Adaptive personality characteristics, including secure attachment style, may offer resilience against the adverse effects of TBI, enhancing adaptive functioning (Sela-Kaufman et al., 2013).

Genetic influences on TBI outcome have been documented in relation to several genes, although the results have been contradictory (Davidson, Cusimano, & Bendena, 2014; Jordan, 2007). Genetic polymorphisms have been indicated to have multifactorial roles in regulating brain responses to TBI (Davidson et al., 2014). One of the most studied genes has been apolipoprotein E (APOE) (e.g. Mahley & Huang 2012; Ponsford et al., 2011) related to decreased growth and branching of neurites. Carriers of APOE ε4 allele have been associated with increased risk of poor long-term outcomes after TBI (for recent review, see Davidson et al., 2014). Although research has produced important views on the relevance of genes and TBI outcome, currently no clear testing protocol exists for TBI patients (Maas et al., 2017).

Among factors related to injury, TBI severity has been shown to be one of the most robust predictors of outcome (e.g. Ponsford et al., 2016; Rassovsky et
Length of PTA has been well-documented to correlate with functional outcome, independent living, productive activity, cognitive impairment, and life satisfaction (e.g. Brown et al., 2005; Hart et al., 2016; Kosch et al., 2010; Nakase-Richardson, 2011; Sherer et al., 2008; Walker et al., 2010). Findings from a recent Traumatic Brain Injury Model Systems (TBIMS) study (Walker et al., 2018) indicated PTA duration to be the most critical outcome predictor of long-term functional outcome after moderate to severe TBI. GCS score is apparently less beneficial in predicting late outcome relative to other TBI severity indicators (Keyser-Marcus et al., 2002; Ponsford et al., 2016; Van der Naalt et al., 1999).

Among the most important postinjury factors, disability level at rehabilitation discharge has shown strong evidence for predicting long-term outcome after TBI (e.g. van Velzen, van Bennekom, Edelaar, Sluiter, & Frings-Dresen, 2009; for reviews, see Ownsworth & McKenna, 2004; Willems-van Son et al., 2007). Cognitive, emotional, and behavioral impairments have been demonstrated to be the most impairing factors related to long-term TBI outcomes (Benedictus, Spikman, & van der Naalt, 2010; Brooks, McKinlay, Symington, Beattie, & Campsie, 1987; May et al., 2017; Rabinowitz & Levin, 2014; for a recent meta-analysis, see Allanson et al., 2017). Moreover, involvement of rehabilitation services based on a comprehensive approach entailing medical, psychosocial, and vocational interventions has been consistently associated with improved productivity, other functional, and life satisfaction outcomes after TBI (e.g. Cicerone et al., 2019; Maas et al., 2017; Patel et al., 2015; van Velzen et al., 2009).

Self-awareness, referring to perceiving changes to one’s self and abilities after TBI (Luria, 1963; Cicerone & Tupper, 1986), is considered a vital factor in influencing participation in rehabilitation, setting realistic goals, developing compensatory strategies, and enhancing psychosocial adjustment (e.g. Ownsworth & Fleming, 2005; Ownsworth & McKenna, 2004; Robertson & Schmitter-Edgecombe, 2015). Greater self-awareness has been shown to be associated with better rehabilitation outcomes after TBI (for review, see Ownsworth & Clare, 2006), including employment, even after controlling for injury severity (Kelley et al., 2014). Improvement in awareness has generally been associated with emotional well-being rather than heightened emotional distress (Malec & Moessner, 2000; Ownsworth & McFarland, 2004).

Continued alcohol or substance abuse after TBI is associated with poorer medical, social, rehabilitation, and vocational outcomes (Draper, Ponsford, & Schönberger, 2007), along with an increased risk of recurrent head traumas (Weil et al., 2016). Impaired executive functioning or attempts to self-medicate for emotional problems may also account for ongoing alcohol and substance abuse postinjury (Weil, Corrigan, & Karelina, 2016). Preinjury abuse has been shown to be highly predictive of problem use after TBI (e.g. Bombardier, Temkin,
Machamer, & Dikmen, 2003; Ponsford et al., 2007). Evidence exists also for alcohol misuse in patients without problem drinking prior to TBI at least in a subset of patients, particularly those injured early in life (Björk & Grant, 2009; Fann et al., 2004; Silver et al., 2001).

Recent research has identified the importance of environmental or contextual factors in TBI outcomes (Hammel et al., 2015; for reviews, see Ciccia & Threats, 2015; Sherer et al., 2015). Regardless of the TBI severity, affected individuals encounter significant environmental barriers to employment, education, community mobility, social integration, and life satisfaction (Whiteneck, Gerhart, & Cusick, 2004; Ciccia & Threats, 2015). The strongest impacts have been related to transportation, surroundings, government policies, attitudes, and the natural environment (Whiteneck et al., 2004). Environmental variables potentially predicting employment after TBI have been identified by Sherer and colleagues (2015) to be access to transportation and disability at rehabilitation discharge and participation in social interaction. Regaining employment after TBI has been found to be related to such environmental factors at work as the possibility to return to the preinjury job, the provision of work trials or modified tasks, and a lengthy period of supported work conditions to help individuals to adapt to their disabilities (Johnson, 1987). Furthermore, insurance status as an economic environmental factor has been noted to be related to TBI outcomes (Patel et al., 2015); privately insured individuals with more access to rehabilitation resources reported improved functional and QoL outcomes than publicly insured ones who may have insurance restrictions and more stressors, including financial strains.

### 1.3.3 GLOBAL OUTCOME

As a complex condition, outcomes following TBI are exceedingly variable depending on numerous influencing factors as well as the selected outcome domain and assessment tool (Maas et al., 2017; Walker et al., 2018). Consequently, individuals with apparently similar TBIs may have substantial variation in outcome (Katz et al., 2013). Global outcome – assessment of the overall impact of TBI incorporating functional status, independence, and participation (Wilde et al., 2010) – can in the long term range from total dependency to good recovery for individuals with moderate to severe TBI (Wilson, Pettigrew, & Teasdale, 1998). TBI on the mild end of the severity continuum can also have persistent and disabling consequences affecting outcome (Levin & Díaz-Arrastía, 2015; McMillan, Teasdale, & Stewart, 2012).

Functional and psychosocial outcomes can improve or deteriorate many years after TBI onset (Corrigan & Hammond, 2013; Dijkers, Harrison-Felix,
Introduction

& Marwitz, 2010; Green, 2015; Ishibe et al., 2009; Maas et al., 2017; Wilson et al., 2017). Data have shown that less than 50% of patients with severe TBI and less than 60% of all TBI patients will have favorable outcome (GOSE ≥5) by one year postinjury (Myburgh et al., 2008). Thornhill and colleagues (2000) found that 52% of patients with severe TBI were moderately to severely disabled at one year postinjury. At five years postinjury, most of the surviving individuals who had received acute inpatient rehabilitation were still moderately or severely disabled (Corrigan et al., 2014). In addition, more than one-third had declined from a previously achieved functional outcome level across all age groups, one-half had been readmitted to hospital, and one-fifth had died (Corrigan et al., 2014). Similarly, Asikainen and colleagues (1998) reported that in the moderate to severe Finnish TBI group at five years or more postinjury 17% were assigned to the category of ‘good recovery’, 49% to ‘moderate disability’, and 34% to ‘severe disability’ based on GOS.

Until recently, longitudinal outcome research beyond five years TBI has been limited. Earlier studies from Brooks (1987), Himanen (2005), Hoofien (2001), Thomsen (1974, 1984, 1992), and Wood (2006a) and their collaborators have provided important information on long-term outcome. At present, the TBIMS database in the United States of America (Dijkers et al., 2010; for more information, see www.tbinds.org and https://msktc.org/tbi/) and a representative cohort identified by Thornhill and colleagues (2000) in Glasgow have enhanced understanding of global outcome changes over time. Both cohorts have allowed follow-ups of more than ten years, TBIMS data for up to forty years. Results suggest that for long-term outcomes of individuals with moderate or severe TBI, change is more common than stability (Corrigan & Hammond, 2013; Dijkers et al., 2010). The typical trajectory of functional status after TBI appears to improve gradually for about ten years, then plateau, followed by deterioration (Dams-O’Connor et al., 2015; Pretz & Dams-O’Connor, 2013; Thornhill et al., 2000). Corrigan and Hammond (2013) found that after ten years post-TBI one in three individuals seemed to deteriorate, and most of them with two categories on the GOSE. McMillan and colleagues (2012) reported that at 12–14 years post-TBI about half of the survivors were disabled, one-quarter had improved, one-quarter had declined, and 16% had died. Factors related to this trajectory of functional outcome are not yet well-known, but have been suggested to include genetic predisposition, presence or absence of medical or psychosocial comorbidities, consistency of follow-up, and lifelong healthcare and disability services (Hammond & Malec, 2016). With the TBIMS data (McMillan et al., 2012; Whitnall, McMillan, Murray, & Teasdale, 2006), delayed improvement and decline were found to be more strongly associated with emotional adjustment, self-esteem, and stress than with injury severity or cognitive impairment. More
than half of the patients were disabled across follow-ups, although the majority of the TBIs were assessed as mild (McMillan et al., 2012; Whitnall et al., 2006).

One of the first follow-up studies of long-term functional outcome comparisons in a sample of moderate to severe TBI was reported by Ponsford and colleagues (2014) at two, five, and ten years postinjury. Fatigue and balance problems proved to be the most common symptoms, reported by 60–70% of the sample, with rates decreasing only slightly across time. Sensory changes, reported by about a third of the sample, seemed to be also quite persistent over time. Changes in a broad range of cognitive functions, communication, behavior, and emotional state were reported by a high proportion, approximately 60% of the sample, at all time points. Irritability was a common and persistent problem, reported by over two-thirds of the sample. Anxiety and depression were reported by almost half of the sample still at ten years after injury. Mobility outcomes, in turn, were good. At ten years postinjury, individuals of the sample with severe or very severe TBI mainly represented vegetative or severe disability, approximately 20% moderate disability, and 15–25% good recovery, while individuals with mTBI evenly showed moderate disability or lower good recovery based on GOSE scores (Ponsford et al., 2014).

1.3.4 PSYCHOSOCIAL OUTCOME

Psychosocial functioning has been demonstrated to be an important TBI outcome domain; however, no consensus exists on its definition. Difficulties in psychosocial functioning typically encompass difficulties in community re-entry (e.g. Sandhaug, Andelic, Langhammer, & Mygland, 2015; Williams et al., 2014) or participation within the community (WHO, 2001 and 2013). Community integration has been defined as an individual’s ability to resume culturally and developmentally appropriate social roles following TBI (Andelic et al., 2016; Corrigan, 1994). A recent review (Shaikh, Kersten, Siegert, & Theadom, 2018) indicated that community integration appears to be more diverse than earlier acknowledged as well as being a nonlinear process reflecting recovery after TBI across time, serial goals, and transitions.

Trajectories have indicated community integration including home integration, social integration, and productive activities, to improve significantly over five years postinjury after moderate to severe TBI (Andelic et al., 2016; Willemse-van et al., 2009). However, community integration has been shown not to be fully accomplished within the five-year period (Andelic et al., 2016). Older age predicted poor and progressively worsening participation, whereas better physical function at discharge from inpatient rehabilitation predicted better
participation over five years after moderate to severe TBI in a large recent sample from the TBIMS database (Erler et al., 2018). Moreover, better cognition, white race, no depression, more years of education, and living with others were noted to be related to better participation regardless of the measurement point (Erler et al., 2018). In the long term (mean 13 years postinjury), 90% of TBI individuals with disability reported dissatisfaction with their social integration (Dawson and Chipman, 1995).

**Independence and living situation.** Approximately 20% of survivors with severe TBI receiving inpatient rehabilitation have been shown to recover to functional independence and to be capable of living without in-house supervision over a period one to five years postinjury (Nakase-Richardson et al., 2012). Corrigan and colleagues (2014) found that at five years postinjury of those receiving acute inpatient rehabilitation, 12% were living in institutional settings. At ten years postinjury, Hoofien and colleagues (2001) noted that about 65% of the patients with severe TBI lived with a spouse, 17% with their parents, 14% alone, 4% shared a residence with a friend, and none lived in nursing homes. A follow-up study of up to ten years postinjury (Ponsford et al., 2016) reported that the majority of the sample of moderate to severe TBI patients were independent in personal daily activities. However, about 40% of them still required more assistance than before the injury.

**Relationships and family functioning.** Over 90% of persons with TBI have reported changes in their friendships, and 75% have had difficulties in making new friends after TBI (Bergland & Thomas, 1991). The number of persons with TBI reporting difficulty in personal relationships showed an increase over time in a sample followed up for ten years postinjury (Ponsford et al., 2016). Around 40–50% reported having lost friends or becoming more socially isolated since injury (Ponsford et al., 2016). Similarly, Hoofien and colleagues (2001) found a relatively high rate of loneliness 10–20 years postinjury.

Caring for people with TBI can potentially be stressful, more taxing, and less rewarding to interact socially, with high levels of long-term psychological burden placed on family members (e.g. Brooks, Campsie, & Symington, 1986; Vangel, Rapport, & Hanks, 2011; Lefebvre & Levert, 2012). Consequently, the risk of breakup of close relationships is increased (Wood & Yurdakul, 1997). In previous studies the marriage rate been has shown to be substantially lower and the divorce rate higher than the national average (e.g. Hoofien et al., 2001; Tate & Broe, 1999; Tate et al., 1989; Thomsen, 1992). However, in a more recent longitudinal study (Ponsford et al., 2014) marital status remained stable over time. Significant impairments in sexual functioning and needs have been found.
after TBI (Moreno, Gan, Zasler, & McKerral, 2015), with nearly 30% of individuals reporting dissatisfaction with sexual function by year one (Sander et al., 2012).

Participation in recreation and leisure activities. Reviews on psychosocial outcomes have demonstrated a decrease in leisure activities for individuals with TBI (Morton & Wehman, 1995; Stocchetti & Zanier, 2016). Individuals with moderate to severe TBI have shown re-integration to their previous levels of leisure and recreation activities in approximately half of the cases at each assessment time point for up to ten years postinjury (Dikmen, Machamer, Powell, & Temkin, 2003; Ponsford et al., 2014). TBI sequelae combined with lost friendships and reduced financial resources may render social and leisure activities challenging, creating also a renewed dependence of the patient on family to meet these needs (Morton & Wehman, 1995).

Participation in work-related activities. Employment rates for persons with TBI vary greatly due to heterogeneity between studies showing differences in patient populations, follow-up times, study designs, methods of operationalizing return to work-related activities, and thresholds of determining the success of return to work (RTW) (Ben-Yishay et al., 1987; Hall & Cope, 1995; Grauwmeijer, Heijenbrok-Kal, Haitsma, & Ribbers, 2012; McKinlay & Brooks, 1984; Odgaard et al., 2017; Saltychev, Eskola, Tenovuo, & Laimi, 2013). Moreover, country-specific social security systems, economic factors, and employment conditions influence employment outcomes after TBI (e.g. Grauwmeijer et al., 2012). Reported employment rates have varied from 0 to 99% over an extended period of time (Brooks et al., 1987; Dikmen et al., 1994; Englander, Hall, Stimpson, & Chaffin, 1992; Gollaher et al., 1998; Grauwmeijer et al., 2012; Hillbom, 1959a, 1959b; Humphrey & Oddy, 1980; McMordie, Barker, & Paolo, 1990; Odgaard et al., 2017; Ponsford et al., 2014 and 2016; Sander, Kreutzer, Rosenthal, Delmonico, & Young, 1996; Schönberger et al., 2011; Stocchetti & Zanier, 2016; Thomas, Burker, & Kazuakauskas, 2015; Wehman, West, Kregel, Sherron, & Kreutzer, 1995). In a review by van Velzen and colleagues (2009), the overall estimate of RTW within two years postinjury was about 40%, ranging widely from 0 to 84%, with a substantial proportion not able to either return to their previous work or stay permanently. Similarly, in a review of Shames and colleagues (2007), RTW rates varied broadly from 12% to 70%, with chronic consequences identified to influence outcomes also in a proportion of mTBI patients (for review, see Stocchetti & Zanier, 2016). In a follow-up study (Ponsford et al., 2014) of up to ten years postinjury, 40% of individuals with TBI had returned to open employment in some capacity. Only a minority of this sample with a considerably decreasing trend over time had returned to full-time employment. Those older than 50
years at injury showed lower employment rate and higher workforce leaving rate at five and ten years postinjury (Ponsford et al., 2014). In a Norwegian population-based study at ten years postinjury even persons of working age with favorable outcomes in GOSE had difficulties in RTW after moderate to severe TBI (Andelic et al., 2009).

The poorest employment rates have been found in individuals with severe TBI (Brooks et al., 1987; Jacobs, 1988; Sandhaug, et al., 2015; Wehman et al., 1995). A nationwide five-year follow-up study in Denmark (Odgaard et al., 2017) reported RTW for severe TBI to be low compared with the general population, with 30% affected individuals attempting to RTW. In a Norwegian sample (Sandhaug et al., 2015), 80% of severe TBI patients were unemployed at two years postinjury. A recent review by Stocchetti and Zanier (2016) found that individuals with severe TBI may sometimes be offered sheltered work but return to prior work positions is rare. Odgaard and colleagues (2015) reported a stable labor market attachment of 16% for severe TBI, which continuously decreased, falling to 11% within five years. Moderately injured TBI patients have been found to have a significantly higher productivity level, including voluntary activities, than severely injured patients in follow-up studies for up to a decade postinjury (Hoofien et al., 2001; Sandhaug et al., 2015). Psychosocial outcome of the Finnish CHRP, INSURE, is evaluated in terms of return to productive activities in Study I.

1.3.5 OUTCOMES FOR SUBJECTIVE WELL-BEING AND QUALITY OF LIFE

The ultimate goal of rehabilitation is to enable individuals with TBI to enhance and maintain the best possible subjective well-being and QoL (Bullinger, 2002; Cicerone & Azulay, 2007; Dijkers, 2004; von Steinbüchel et al., 2012). Subjective well-being has been conceptualized as comprising both affective and cognitive evaluative components (Pavot & Diener, 2008). Life satisfaction represents the evaluative cognitive component and global appraisal of the quality of one’s overall life (Pavot & Diener, 2008). Global appraisal is influenced by satisfaction in those life domains that are most essential to each individual (Diener & Suh, 1998; Dijkers, 2004). Life satisfaction seems to be a critical and fluctuating outcome for persons with TBI with diverse continuous deficits (Dijkers, 2004; Resch et al., 2009). A population-based study by Whiteneck and colleagues (2016) showed that around twice as many persons with all TBI severities reported low life satisfaction and activity limitations after nontreated TBI than their peers with treated TBI in all settings. In a Swedish sample (Jacobsson & Lexell, 2013), individuals admitted to hospital after TBI reported at 6–15 years postinjury significantly worse life satisfaction overall and specifically related to vocation,
leisure, ADL, and somatic and psychological health than the reference sample. The moderate to severe TBI group rated their life satisfaction significantly lower for vocation, ADL, and psychological health, whereas the mTBI group reported significantly lower life satisfaction regarding life overall, and specifically somatic health (Jacobsson & Lexell, 2013).

Factors related to QoL after TBI. TBI has been found to encompass a broad spectrum of HRQoL, with most problems reported in the domains of emotional, social, and physical functioning (for review, see Polinder et al., 2015). HRQoL after TBI has been shown to be related to a wide variety of factors, including emotional status (e.g. Haagsma et al., 2015; Jakobsson, Westerberg, Malec, & Lexell, 2011; Siponkoski, Wilson, von Steinbuechel, Sarajuuri, & Koskinen, 2013), sense of coherence (e.g. Jakobsson et al., 2011), perceived self-efficacy (e.g. Cicerone & Azulay, 2007; Rutterford & Wood, 2006), behavioral disturbances (Ergh, Hanks, Rapport, & Coleman, 2003; Koskinen, 1998; Jorge, 2005), cognitive deficits (e.g. Kozlowski, Pollez, Thevenon, Dhellemmes, & Rousseaux, 2002), sleep disturbances and fatigue (e.g. Baumann, Werth, Stocker, Ludwig, & Bassetti, 2007; Cantor et al., 2008), pain (e.g. Hoffman et al., 2007; Branca & Lake, 2004), impaired communication skills (e.g. Dahlberg et al., 2006), loss of independency in ADL skills (e.g. McCarthy et al., 2006; Mailhan, Azouvi, & Dazord, 2005; Siponkoski et al., 2013), comorbid health conditions (e.g. von Steinbuechel, et al., 2010), changes in participation (e.g. Jakobsson et al., 2011; Pierce & Hanks, 2006), vocational status (e.g. Thomas et al., 2015; Cicerone & Azulay, 2007), and overall psychosocial functioning (e.g. Williams, Rapport, Millis, & Hanks, 2014) as well as gender, age at injury, education level, injury severity, and time since injury (e.g. Cicerone & Azulay, 2007; Jacobsson & Lexell, 2013; Siponkoski et al., 2013; Truelle et al., 2010). TBI has been shown to have a stronger negative impact on mental HRQoL than on physical HRQoL (for review, see Polinder et al., 2015). The most affected domains of QoL after TBI have been confirmed to be social function, emotions, and mental health (for review, see Stocchetti & Zanier, 2016).

Trajectories of life satisfaction following TBI. Life role participation and depressive symptoms have been found to be robust predictors of life satisfaction across the first five years post-TBI (Juengst et al., 2015). Individuals with loss of life roles and depressive symptoms after TBI were at a particularly high risk for low or declining life satisfaction (Juengst et al., 2015). Studies examining trajectories of life satisfaction over time after TBI have reported incoherent results in the early postinjury period as well as in the long-term (Andelic et al., 2009; Cicerone & Azulay, 2007; Evans, Sherer, Nakase-Thompson, Novack, &
Nick, 2005; Jakobsson et al., 2011; Mailhan et al., 2005; Polinder et al., 2015; Siponkoski et al., 2013). Cicerone and Azulay (2007) found a significant relation between life satisfaction and time postinjury, revealing that patients at less than one year postinjury had significantly higher QoL. Corrigan and colleagues (1998) found that early life satisfaction declined in the first years after discharge from inpatient rehabilitation. Higher QoL in the early stage has been interpreted to be a result of impaired self-awareness (Evans et al., 2005) or to represent the period when patients have not yet encountered the full influence of TBI on their life (Corrigan, Smith-Knapp, & Granger, 1998). Reviews of up to ten years after TBI (Polinder et al., 2015) have demonstrated reduced HRQoL during and after the first postinjury year to be a common finding after TBI. Significantly decreased HRQoL was also found ten years postinjury among a Norwegian working-age population hospitalized in the acute stage with moderate to severe TBI (Andelic et al., 2009). In a Finnish sample, with all TBI severity levels receiving multidisciplinary residential rehabilitation, QoL remained relatively stable up to 15 years postinjury (Siponkoski et al., 2013). Some studies, in turn, have shown life satisfaction to improve with time after TBI (e.g. Andersson, Bedics, & Falkmer, 2011; Brown et al., 2011; Corrigan et al., 1998; Jacobsson et al., 2011; Wood, 2008). Reasonable long-term satisfaction with life up to 17 years after severe TBI was described by Wood and Rutterford (2006a). Life satisfaction appears to be dynamic and may rebound as gradual adjustments to the effects of TBI are made over time particularly regaining social participation seems to contribute significantly to life satisfaction many years after TBI (Cicerone & Azulay, 2007; Jacobsson & Lexell, 2013).

Perceived self-efficacy, especially in the management of cognitive deficits, has been found to be a significant predictor of global life satisfaction across time (Cicerone & Azulay, 2007; Wood & Rutterford, 2006a; for meta-analysis, see Holden, 1991). Moreover, perceived self-efficacy has appeared to mediate the relationships between cognitive functioning and life satisfaction (Wood & Rutterford, 2006a) and community integration and global life satisfaction (Cicerone & Azulay, 2007).

**Associations between life satisfaction and community integration after TBI.** Although life satisfaction and QoL have in some studies been found to be related to level of community functioning, there is evidence that they represent independent outcomes after TBI (Corrigan, 2004; Cicerone & Azulay, 2007). Heinemann and Whiteneck (1995) found a positive relation between global life satisfaction and social integration and productivity. Corrigan and colleagues (2004) observed that life satisfaction was only modestly related to factors predicting other domains of TBI outcomes. Smith and colleagues (1998), in turn, found no relationship
between subjective well-being and community integration in the long term. Nor did Burleigh and colleagues (1998) find any relation between life satisfaction and home integration, community integration, and productivity, but did observe a modest relation with social integration. Overall, only minor or modest associations have been found between long-term life satisfaction and community integration (Cicerone, Mott, Azulay, & Friel, 2004; Cicerone & Azulay, 2007; Corrigan, Bogner, Misyiw, Clinchot, & Fugate, 2001).

1.3.6 SUBJECTIVE APPRAISAL OF OUTCOMES

Traditionally, the focus in assessing the effects of rehabilitation and outcomes after TBI has been on objective and external measures such as psychometric test performances (e.g. van Heughten, Caldenhove, Crutsen, & Winkens, 2019), functional level (e.g. Sandhaug, Andelic, Berntsen, Seiler, & Mygland, 2011), community integration (e.g. Dijkers et al., 1997; Salter, Foley, Jutai, Bayley, & Teasell, 2008), social participation (e.g. Cicerone, 2004; Jones & Curtin, 2010), or participation in work-related activities (e.g. Corrigan et al., 2007; Odgaard et al., 2017). However, over the past decade there has been increasing awareness of supplementing outcome assessment by subjective, experiential measures reflecting the patient’s perspective (e.g. Ben-Yishay & Daniels-Zide, 2000; Dijkers, 2004; von Steinbuechel et al., 2012).

Only a few studies have explored both objective assessment of activity or psychosocial outcomes and patients’ subjective weightings of these outcomes (Brown et al., 2004; Curtin et al., 2011; Johnston, Goverover, & Dijkers, 2005; Laman & Lankhorst, 1994). Stineman and colleagues (2003) reported differences in patients’ subjective valuation of the same numeric functional status score in the Functional Independence Measurement (FIM). Johnston and collaborators (2005) explored subjective feelings in areas of community integration using a ‘delighted’–’terrible’ scale. Results showed only a weak and incongruent relation across individuals between subjective appraisals and objective measures of work life, social life, mobility, and economic status (Johnston et al., 2005). Ben-Yishay and colleagues (2010) sought to explore whether their hypothesized association between an objective outcome (level of work or productivity) of CHRP and six subjective measures of self-appraisal (effort during rehabilitation, meaning in life, productivity, acceptance, social life, and intimate relationships) would be confirmed in a multinational, unpublished pilot study of 201 TBI patients. They found that the level of work accomplished after CHRP was associated with how patients rated themselves in the six subjective areas of self-appraisal (Ben-Yishay et al., 2010).
In summary, very little is currently known about the relationship between assessment of components of community integration and their subjective appraisal by individuals with TBI. Moreover, current research has shown a discrepancy between study findings, indicating that higher levels of community integration will not necessarily be valued by the TBI individuals themselves, and thus, may not be enough to provide life satisfaction (Johnston et al., 2005). Incongruent relations between objective measures of psychosocial outcomes and their subjective appraisals can be regarded as a fundamental challenge for evaluations of TBI outcomes and may have important implications for the allocation of different rehabilitation interventions. This topic is addressed in Study III.
2 AIMS OF THE THESIS

This thesis describes an application of a CHRP method, the Individualized Neuropsychological Subgroup Rehabilitation Program (INSURE) (Kaipio, Sarajuuri, Koskinen, 2000), and explores its contribution to psychosocial outcomes and the subjective self-appraisal of these outcomes in adults with postacute TBI. Also evaluated was the relationship between cognitive and motor functions for its clinical implications on multidisciplinary neurorehabilitation after TBI. Specific objectives of Studies I-III were as follows.

Study I evaluated the outcome of an application of a CHRP in TBI by comparing productivity of patients who underwent CHRP with that of matched control patients who received conventional clinical care and rehabilitation. After completion of the CHRP, patients were followed up for two years and then evaluated for their long-term outcome.

Study II explored the relationship between cognitive and motor performance in patients with TBI for its potential clinical implications on multidisciplinary rehabilitation. Cognitive functioning was measured in the domains of information processing, attention, and executive functions, particularly in regulation of voluntary movements. Motor performance was measured in terms of postural balance, agility, and gross motor rhythm coordination. This explorative study was intended to provide additional guidance for further research on the relationship between cognitive and motor performance, and to enhance understanding of the multimodal sequelae of TBI with regard to multidisciplinary TBI rehabilitation.

Finally, Study III, explored the relationship between objectively measured outcomes of neurorehabilitation and their subjective self-appraisal in individuals with TBI who had resumed working at various levels of competence following a CHRP. The specific aim was to re-examine the claim of Ben-Yishay and collaborators (2010) that the objective outcomes (level of work) were associated with subjective areas of self-appraisal (effort during rehabilitation, meaning in life, productivity, acceptance, social life, and intimate relationships) in individuals with TBI who had undergone a CHRP as well as to evaluate the implications of these findings for the relevant targeting of rehabilitation interventions.
3 METHODS

3.1 STUDY I

3.1.1 PARTICIPANTS

Nineteen patients with the primary diagnosis of TBI consecutively admitted to the INSURE program at the nationwide Käpylä Rehabilitation Centre, in Helsinki, Finland, served as the rehabilitation patients (treatment group). The inclusion criteria were (1) independence in daily life and only slight physical disabilities, (2) 16–55 years of age, (3) completed compulsory education, and (4) adequate potential to achieve productivity if given special rehabilitation. Patients were excluded if they presented (1) a significant psychiatric history, (2) alcohol or drug abuse, (3) a previous brain injury, or (4) another malignant disease during follow-up.

Control patients were selected from 213 patients with TBI who were seen for neuropsychologic examination in a level I trauma center at Helsinki University Hospital and who had their TBI during the same time period as the treatment patients. Using the same inclusion and exclusion criteria as in the treatment group, 23 patients were selected. The control patients were selected to make this group as similar as possible to the treatment group with respect to age, sex, education level, injury severity (based on GCS and radiologic, neuropsychologic, and neurosurgical findings), time from injury to evaluation, and preinjury employment status. All control patients were considered potential candidates for the INSURE program based on the medical files and clinical judgment of a senior neuropsychologist in the program and the neuropsychologist who had examined them in the trauma center. According to a routine policy, TBI patients are transmitted to their local health care units responsible for the continuation of their care and rehabilitation after the acute care in the trauma center at the Helsinki University Hospital. Three of the control patients were later lost to follow-up.

Demographic and injury-related information obtained from hospital files is given in Table 1. The neuropsychologic sequelae of patients in both groups consisted of various combinations of deficits including (1) tendency for fatigue, (2) slowness of information processing, (3) attention and concentration, (4) learning and memory, (5) executive skills (e.g. difficulties in initiation, planning, and self-monitoring or in judgment), (6) modulating affective states (e.g. irritability and emotional lability), and (7) language communication (e.g. tangentiality, hyperverbality, and ineffective word retrieval). Table 2 presents rehabilitation
before and after the CHRP as the follow-up support therapies for the treatment group patients. Many of these patients had received a lot of rehabilitative care conventionally available in the healthcare system. Six (32%) of them had also attempted to return to work or education one or more times but had failed. Six (30%) of the control patients had attempted but failed to return to work after their TBI.

**Table 1.** Comparison of Treatment and Control groups regarding demographic and injury-related characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment group (n = 19)</th>
<th>Control group (n = 20)</th>
<th>U&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at injury, years</td>
<td>30.5±10.6 (16.0−52.0)</td>
<td>29.5±11.0 (17.0−54.0)</td>
<td>0.52</td>
<td>0.60</td>
</tr>
<tr>
<td>Education, years</td>
<td>11.3±2.0 (9.0−17.0)</td>
<td>12.2±2.9 (8.5−18.0)</td>
<td>0.76</td>
<td>0.45</td>
</tr>
<tr>
<td>Admission GCS score</td>
<td>7.9±2.7 (4.0−14.0)</td>
<td>8±2.5 (3.0−13.0)</td>
<td>−0.32</td>
<td>0.75</td>
</tr>
<tr>
<td>Chronicity, months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42.4±17.7 (28.0−106.0)</td>
<td>46.6±20.2 (25.0−119.0)</td>
<td>−0.98</td>
<td>0.34</td>
</tr>
<tr>
<td>Men/women</td>
<td>16/3</td>
<td>17/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment status, n&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16</td>
<td>17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Injury mechanism, n**

| Injury mechanism                        | Treatment group | Control group | |
|-----------------------------------------|-----------------|---------------|
| Motor vehicle collision                 | 8               | 7             |
| Bicycle collision                       | 3               | 1             |
| Pedestrian-auto collision               | 1               | 3             |
| Assault                                 | 1               | 1             |
| Other, fall, hit by an object           | 5               | 8             |
| Unknown                                 | 1               | 0             |

**CT/MRI findings, n**

| CT/MRI findings                         | Treatment group | Control group | |
|-----------------------------------------|-----------------|---------------|
| Contusion and/or intracranial hematoma   | 15              | 16            |
| Diffuse axonal injury                   | 8               | 5             |
| Signs of severe intracranial pressure   | 7               | 5             |
| Craniotomy                              | 4               | 5             |

NOTE: Values are mean ± standard deviation (range) in parentheses unless otherwise indicated. Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

<sup>a</sup> Mann-Whitney statistic.

<sup>b</sup> Time from injury to 2-year follow-up evaluation.

<sup>c</sup> Patients who were employed or studying preinjury.
Table 2. Pretreatment and postdischarge follow-up therapy for patients in the Treatment group (n = 19).

<table>
<thead>
<tr>
<th>Type of rehabilitation</th>
<th>Before n (%)</th>
<th>Follow-up n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational therapy</td>
<td>6 (32)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>9 (47)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Speech therapy</td>
<td>5 (26)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neuropsychological rehabilitation</td>
<td>7 (37)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Inpatient rehabilitation center</td>
<td>11 (58)</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Outpatient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational therapy</td>
<td>2 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>4 (21)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Speech therapy</td>
<td>2 (11)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Neuropsychological rehabilitation</td>
<td>14 (74)</td>
<td>16 (84)</td>
</tr>
<tr>
<td>Revision of the program</td>
<td>NA</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

3.1.2 INTERVENTIONS

The INSURE program is an application of the CHRP method (Kaipio et al., 2000) that is six weeks in length and is provided to selected groups of inpatients with TBI. It is based on the pioneering works of Goldstein (1942, 1952, 1959), Ben-Yishay and colleagues (1985, 1987), Prigatano and colleagues (1986, 1994), and Christensen and colleagues (1992).

In the INSURE program, each rehabilitation group of the program consists of 5–8 members to ensure intense working conditions. To facilitate peer solidarity and support, special care is taken in the selection process of the patients to ensure that the groups are as homogenous as possible in terms of age, education, and nature of injury. Also, the critical nature of personal commitment is emphasized during the recruitment interview.

The daily schedule of the program runs from 8:30 AM to 4:00 PM on weekdays. Therapy interventions are carried out in individual and group formats. Although the program is standardized, it is also individualized concerning the allocation of different individual therapies to meet the special needs of each patient. The staff includes neuropsychologists, neurologists, rehabilitation nurses, social workers, speech and language pathologists, occupational therapists, and physical therapists. Medical consultations are arranged, usually with specialists in neuropsychiatry, neuroradiology, and phsiciatry. The staff works closely together to foster consistency among the various activities.
The days begin with a group meeting called the Orientation group. In this meeting, the participants with the neuropsychologists determine individual goals for the day and the program. As the program continues, long-term goals are set. Another aim of the meeting is to promote both psychological and physiological arousal and to foster personal orientation.

The neuropsychological Psychotherapy group meets four days a week. The group involves discussions on injury-related pathophysiological, neuropsychological, and neurobehavioral aspects of TBI as well as on personal reactions, coping, and psychosocial adjustment. The group aims at increasing patients' understanding of the nature of TBI sequelae and their impact on patients' emotions, social lives, and coping with the deficits and stress caused by TBI. The participants also have individual neuropsychotherapy sessions daily. They are taught to assess their goals for work and education realistically, bearing in mind the postinjury changes in their resources.

The Cognitive group aims to help participants to (1) understand the rationale for cognitive remedial training capable of ameliorating the interferences of attentional disorders, poor information processing abilities, and memory problems with reasoning functions, (2) practice compensatory skills capable of enhancing cognitive skills, and (3) translate lessons learned from the rehabilitation setting to daily life. The implications of neuropsychological changes are considered in terms of recovery, compensation, and functional obstacles. Computer-administered cognitive remediation software, including active therapist involvement, is used as a tool (Koskinen & Sarajuuri, 2004) in the Cognitive group which takes place twice a week.

Various other weekly group activities are used to reinforce the program, which as a whole simulates the conditions and stress of normal working and the challenges of social interaction in everyday life. Enjoyment of life, motivation, and the pleasures of friendship and society are emphasized in planning activities. In the Pragmatic group, speech and language pathologists coach the patients to master pragmatic communication disorders in order to learn to communicate more effectively. The Pictures-of-Self group enables the patients to express their emotions and experiences about the changes in their lives caused by TBI. These sessions help them in the process of self-examination by means of collages made up of different materials such as photos, fabrics, and mosaics. The patients are guided to focus on meaningful childhood memories, express feelings about their families, recall personally meaningful achievements, and examine their progress in rehabilitation. As the patients review their presentations in the group to each other, they may gain better insights into, and control over, their lives, which may, in turn, help them to further diminish confusion and psychological stress related to TBI and its consequences. The Quality-of-Life
group deals with social and material issues related to everyday life and good health practices. The Sport, Relaxation, and Jogging groups aim to encourage the members to start or restart sport activities. Particular attention is also paid to possible TBI-associated injuries or symptoms, such as cervical injuries, pain, sleep disturbances, and posttraumatic stress disorders.

Participation of the significant others is a crucial part of the program. After four weeks, a two-day seminar is held. Patients, their significant others, employers, and professionals from the public healthcare system, are called together to share information and to learn about experiences following TBI. During the seminar each participant also attends a meeting in which his/her plan for continuing rehabilitation is adjusted. Former participants of the INSURE program are also invited to present in the seminar their experiences postdischarge. Such presentations offer the current participants concrete examples of adjustment after rehabilitation. The successful former patients are viewed by the other participants as positive role models.

An essential element in the INSURE program is the supported and tailored vocational interventions aimed at helping the patients to find productive activities that suit their interests and abilities after TBI. Considered as an adapted goal, the patients are encouraged to have supported work trials in the general job market where they could potentially continue afterwards. These interventions are organized with local social and health care units and the compensation system liable for their care. During the program recommendations are made concerning follow-up support, which is arranged through public or private healthcare services. Most patients continue with individual neuropsychological rehabilitation for different periods after completing the program. On completion of the INSURE program, the patients should have substantial knowledge about TBI. This gives them a sound basis for understanding and coping with TBI-related changes in their lives and for participating in productive living according to their own best self-interests.

Control group patients in the study received conventional clinical care and rehabilitation by referral of physicians in the local healthcare system and depending on the compensation system liable for care in each case. The treatment included therapies such as physical, occupational, speech, neuropsychologic, and psychotherapy during hospital care or later in the outpatient format; evaluations of rehabilitation needs; multidisciplinary inpatient rehabilitation in rehabilitation centers; and outpatient follow-ups. By and large, rehabilitation services are individually tailored and delivered in an unstructured and nonsystematic way in the healthcare system. Detailed information on the treatments of control patients was not collected.
3.1.3 MEASURES AND PROCEDURES

A structured self-completion questionnaire covering different areas of productive activities (full- or part-time employment, studying, household management, supported or sheltered work, work trials, voluntary work) was sent to patients and their significant others two years after completion of the program. They were asked to evaluate the primary productive activity in which the patient was engaged just before the injury and at the time of the follow-up evaluation. The controls and their significant others were also asked with the same questionnaire to evaluate the productive activities in which the patient was engaged just before the injury and after the same time interval from injury to outcome evaluation as that of the treatment group. If they did not respond, they were reminded by letter or telephone. In cases of inadequate or unclear information, patients and their significant others were interviewed by telephone. Three controls were met face to face to fill in the questionnaire. All 19 patients in the treatment group and 18 of their significant others returned the questionnaires. In the group of 23 control patients, the respective numbers were 20 and 15.

The outcome was evaluated as productive or nonproductive. Productivity was defined as working (from full-time gainful work to supported work or work trial), studying, or participating in meaningful organized voluntary work. Two neuropsychologists who were not in any other way involved in the study or in patients’ care and rehabilitation and who did not know what kind of rehabilitation each patient had received independently assessed patients’ productivity statuses by analyzing the questionnaires.

3.1.4 STATISTICAL ANALYSES

To compare the two groups of patients, we used the Mann-Whitney U test and the Chi-square test for independent samples. Because the injury-related and demographic variables might have confounded the effect of rehabilitation on outcome, their effects were studied by means of a logistic regression analysis (Armitage et al., 2002). The primary measure of the effect obtained from the logistic model consisted of the odds ratio (OR) and the consequent 95% confidence intervals (CIs). Two-tailed tests were used. The SPSS software package version 12.0.1 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.
3 Methods

3.2 STUDY II

3.2.1 PARTICIPANTS

Men with a primary diagnosis of TBI consecutively attending the nationwide Käpylä Rehabilitation Centre, Helsinki, Finland, and fulfilling the inclusion criteria for the study were recruited over one year. Eligibility for the study in terms of the type and time of injury was verified from medical files. A total of 41 patients with TBI were interviewed on the first day of their rehabilitation period in the center to ensure their suitability for the study. The inclusion criteria were (1) age 19–55 years, (2) body mass index (BMI) less than 35 kg/m², (3) normal Mini Mental State Examination (MMSE; normal > 24/30), a widely used method for screening mental status in adults, testing orientation, attention, immediate and short-term recall, language, and the ability to follow simple verbal and written commands (Folstein et al., 1975), (4) ability to maintain initial test positions, (5) ability to perform a 2 km Walk Test (Laukkanen, 1993), and (6) ability to run a short distance, which was also the criterion for patients to be considered physically well-recovered. Furthermore, the patients had to be more than one year postinjury.

Of the 41 recruited patients, two refused to participate in the study and five did not meet the inclusion criteria. In total, 34 men met the criteria. All patients gave their informed consent. Demographic and injury-related information is shown in Table 3. The study protocol was approved by the Ethics Committee of Ophthalmology, Otorhinolaryngology, Neurology and Neurosurgery of the Helsinki and Uusimaa Hospital District, Finland.
### Table 3. Demographic and injury-related characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TBI group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 34)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>35 (10)</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
<td>177 (7)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>80 (15)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>25.5 (3.9)</td>
</tr>
<tr>
<td>Education, years, mean (SD, range)</td>
<td>11.3 (1.4, 8–12)</td>
</tr>
<tr>
<td>Time from injury, months, median (range)</td>
<td>24 (12–144)</td>
</tr>
<tr>
<td><strong>Injury mechanism, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Motor vehicle collision</td>
<td>18 (53)</td>
</tr>
<tr>
<td>Falling</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Pedestrian-auto collision</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Assault</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Bicycle collision</td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>Glasgow Coma Scale score</strong></td>
<td></td>
</tr>
<tr>
<td>Mild (13–15)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Moderate (9–12)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Severe (3–8)</td>
<td>15 (44)</td>
</tr>
<tr>
<td><strong>Posttraumatic amnesia, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Mild (&lt;24 hours)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Moderate (1–7 days)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Severe (&gt;7 days)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Very severe (&gt;4 weeks)</td>
<td>16 (47)</td>
</tr>
<tr>
<td><strong>CT/MRI findings, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Contusion and/or intracranial hematoma</td>
<td>26 (77)</td>
</tr>
<tr>
<td>Diffuse axonal injury</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Signs of severe intracranial pressure</td>
<td>4 (12)</td>
</tr>
<tr>
<td><strong>Neurosurgical treatment, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Craniotomy</td>
<td>2 (6)</td>
</tr>
<tr>
<td><strong>Type of rehabilitation after injury, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td></td>
</tr>
<tr>
<td>Neuropsychological rehabilitation</td>
<td>24 (71)</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>14 (41)</td>
</tr>
<tr>
<td>Speech therapy</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Occupational therapy</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Inpatient rehabilitation</td>
<td>6 (18)</td>
</tr>
<tr>
<td><strong>Medical treatment for sleeping, mood problems, or pain, n (%)</strong></td>
<td>19 (56)</td>
</tr>
</tbody>
</table>

Abbreviations: TBI, traumatic brain injury; SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging.

* GCS scores were registered at acute hospital phase in 26 patients’ medical files; registration was missing in 8 patients’ files.
3.2.2 MEASURES AND PROCEDURES

Procedures. CT and MRI scans, information concerning GCS scores, neurosurgical interventions, and the length of PTA were evaluated from medical files by a neurologist. A neuropsychologist verified the previous neuropsychological sequelae of the patients from medical files. Various combinations of problems were identified, including (1) a tendency to become fatigued, (2) slowness of information processing, (3) disorders in attention and concentration, (4) disorders in learning and memory, (5) disturbances in executive skills, such as initiation, planning, and self-monitoring, or in judgment, (6) difficulties in modulating affective states, including irritability and emotional lability, and (7) disorders in language communication such as tangentiality, hyperverbal, and ineffective word retrieval. The cognitive examination was conducted after the recruited patients had given their informed consent on the first day of their rehabilitation period. Motor performance was evaluated based on five tests measuring balance, agility, and rhythm coordination. Before starting, the tester demonstrated the performance of each test and the patients were allowed to practice it once. Two experienced physiotherapists administered the tests.

Measures of neuropsychometric testing. On the basis of the very few studies examining the relationship between cognitive and motor performance in patients with TBI, neuropsychological measures of information processing, attention, and executive functions were assumed to show a positive relationship with motor acts in terms of speed and fluency, particularly when attention is divided and the regulation of voluntary movements is required (Cantin et al., 2007; Geurts et al., 1999; McCulloch et al., 2010; Valée et al., 2006). Trail Making tests (TMTs) (Lezak et al., 2004) and the Digit Symbol subtest from the revised Wechsler Adult Intelligence Scale (WAIS-R) (Lezak et al., 2004; Wechsler, 1981) were applied to assess attention, complex information processing, visual conceptual understanding, visuomotor tracking and cognitive flexibility.

The motor function subtests (11 tasks) and acoustico-motor organization subtests (3 tasks) from Luria’s Neuropsychological Investigation (LNI) (Christensen, 1979; Lezak et al., 2004) were used to assess the motor regulation and praxis of the upper limbs. The motor-function subtests used in this study comprised four tasks of simple forms of praxis (separating and bringing together the fingers of both hands, reproducing two positions of the hand shown by the examiner, reproducing particular positions of the hands demonstrated by the examiner while sitting facing the subject, and reproducing the positions of the hands of the examiner while sitting facing the patient and touching the ipsilateral or contralateral ear and eye); two tasks of complex forms of praxis (carrying out an action with objects that are not present, including showing
how to pour and stir tea, thread a needle, and cut with scissors, performing
symbolic actions, threatening [shaking a fist] and waving goodbye); three tasks
of dynamic organization (placing both hands in front, one with the fist clenched
and the other with the fingers outstretched, and then simultaneously changing
the positions of both hands, placing the hands successively in three different
positions (making a fist, extending the fingers with the palm vertical and resting
flat on a table), drawing a design comprising two alternating components; and
two tasks requiring speech regulation of motor acts (knocking twice when the
examiner knocks once and vice versa, and showing a finger when the examiner
shows his fist, and vice versa). The acoustico-motor subtests comprised two
tasks on the perception of rhythmic structures (counting the number of taps
included in single groups of two or three rhythmic taps and counting the number
of taps included in series of groups), and one task requiring the reproduction of
rhythmic structures from a pattern presented acoustically.

Additionally, to get an overview of the patients’ other cognitive functioning
a cognitive screening battery from the Consortium to Establish a Registry for
Alzheimer’s Disease (CERAD) (Moms et al., 1989; Welsh et al., 1994) was used.
The CERAD battery consists of tests of verbal fluency, the modified 15-item
Boston Naming Test, word-list learning, recall and recognition, constructional
praxis and its recall, and the MMSE. The range of the MMSE was restricted
because it was also used as an inclusion criterion.

The results of the verbal-fluency, word-list recall, and constructional praxis
tasks were dichotomized into the categories Normal and Pathological in
accordance with the cutoff scores of the CERAD test. A similar categorization
was used for motor functions of the hands, speech regulation of motor acts,
and perception and reproduction of rhythmic structures. In line with the LNI,
the performance was categorized as Pathological even if only one of the tasks
of a certain function was failed (Christensen, 1979; Lezak et al., 2004). To
be considered Normal, the participant had to perform the tasks without any
difficulty. Given that the scoring in the reproduction of rhythmic structures
test is based on the number of faultless trials in proportion to the maximum
number of trials, a dichotomous variable was formed: Normal: six to seven
points; Pathological: zero to five points.

Measures of motor performance. Indications of static and dynamic postural
instability, retarded velocity, and difficulties in motor coordination have been
reported in TBI patients with good motor recovery, leading to recommendations
in the literature to assess balance, gait, coordination, rapid alternating
movements and proprioception among well-recovered patients (Basford et al.,
2003; Campbell, & Parry, 2005; McFadyen et al., 2003). The chosen motor
tests have proved to be reliable for assessing mild physical impairment after TBI (Vartiainen, Rinne, Lehto, Pasanen, Sarajuuri, Alaranta, 2006). In the static balance test (Suni et al., 1998), the patients stood on one leg with eyes open and arms relaxed by sides. They placed the heel of the opposite foot against the medial side of the supporting leg at the level of the knee joint and kept the thigh rotated outwards. The uppermost limit for the trial was 60 s and the time was measured in seconds on a stopwatch. If this limit was not reached during the first trial, a second trial was allowed. The better result of two trials was used in the statistical analyses. The test was performed separately on each leg, starting with the right leg. The first test of dynamic balance involved tandem walking forwards (Rinne, Pasanen, Miilunpalo, & Oja, 2001). The patients were instructed to place one foot in front of the other with the heel and toe of their shoes touching, and to walk as quickly as possible along a line six meters long without touching the sides or making mistakes in the tandem steps. The test was performed three times and the walking time for each trial was measured. The best result of the three trials was used in the analyses. The second dynamic balance test involved tandem walking backwards (Suni et al., 1998). The instructions were the same as in the first test, but the walking direction was backwards. The best result of three trials was used in the analyses. As a test of speed of the whole-body movement and agility, patients were asked to run as fast as possible in a figure-of-8 (Tegner, Lysholm, Lysholm, & Gillquist, 1986). The course was marked with two traffic cones placed 10 m apart, with the start/finish line next to one of the cones. The stopwatch was started on the starting signal and was stopped when the participant completed the course and crossed the start/finish line again. The test was performed three times with a short rest period between each trial. The best result of the three trials was used in the analyses. The rhythm coordination test (Rinne et al., 2001) consisted of slow and fast phases. The slow rhythm comprised two consecutive parts, each lasting 30 s, and the tester scored the performance on each part in points. The patient was asked first to march on the spot in time to a metronome signal (92 beats/min), one step for each single beat for 30 s, and then to continue marching for another 30 s and to clap his hands together on every other beat. Points were given for both parts separately according to: (1) accuracy in the first 10 s: 0, totally asynchronous marching; 1, gradually getting into the marching rhythm during the first 10 s; 2, a synchronous marching rhythm at the first attempt; and (2) maintenance of the exact rhythm from 10 to 30 s: 0, totally asynchronous rhythm coordination while marching and clapping; 1, difficulties in keeping to the rhythm; 2, maintaining an accurate marching and clapping rhythm for the rest of the test. The sum of the scores in the slow rhythm phase was thus zero to eight points. The fast rhythm phase (138 beats/min) started
immediately after the slow phase. The same procedure was repeated to the rhythm of the metronome. The sum of the scores in this phase was also zero to eight. The sum of both rhythm test scores (0–16 points) was calculated and used in the analyses.

### 3.2.3 STATISTICAL ANALYSES

The means, standard deviations (SDs), medians, ranges, and frequencies are presented as descriptive statistics. Spearman’s partial rank correlation coefficients were used to identify the associations between the continuous neuropsychological tests and the dynamic balance, agility, and rhythm coordination tests. Rank correlations were used due to non-normality in most neuropsychological and motor performance variables. Adjustment was made for the possible confounding variables of age, length of education, PTA, and time from injury. Ranks rather than original values were used in computing the partial correlation coefficients and their 95% CIs in all variables. Scatter-plots of the original values are presented for variables with the highest correlations.

Results of the following neuropsychological tests were dichotomized into categories of normal and abnormal performance: all of the CERAD subtests, except word-list-learning and copying figures (Moms et al., 1989; Welsh et al., 1994), and the subtests of the LNI (Lezak et al., 2004; Wechsler, 1981). The distributions of the motor performance test results in the subcategories (normal/pathological) of the neuropsychological tests are described as box-and-whisker plots. Analyses of covariance, adjusted for the same confounders, were used to study the differences in dynamic balance, agility and rhythm coordination between the normal and the pathological results in the neuropsychological tests. The distributions of the dynamic balance and agility test variables were positively skewed, and thus, the underlying assumptions of normality and equal group variance were not fulfilled. To achieve closer agreement, the variables were log-transformed for the analyses. Adjusted geometric mean ratios (GMRs) were calculated as antilogs of the mean between-group differences in the log-transformed variables. GMR describes the relative difference in group means, with a value of one indicating that there is no between-group difference. The sum score of the rhythm coordination tests was used in the original scale and the result presented as an adjusted between-group mean difference. The 95% CIs of the GMRs and the mean differences are also presented as an indication of the precision of the estimates. Some of the variables in the analyses of the neuropsychological tests were combined because of a high correlation with each other or a low frequency of abnormal results. The LNI motor function
Methods

Subtests comprised four tasks of simple forms of praxis and two tasks of complex forms. These tasks, all measuring praxis of the upper limbs, were first analyzed as separate neuropsychological test variables, but then combined because of their low frequency. The results of the static balance tests were dichotomized into categories of 60 s and below 60 s. Logistic regression analysis was used to examine the associations between the neuropsychological tests and the static balance tests when the neuropsychological variables were considered to be continuous, and Fisher’s exact test when they were categorical (normal/pathological). STATA statistical software version 10 was used for the statistical analyses.

3.3 STUDY III

3.3.1 PARTICIPANTS

The study sample consisted of adults with TBI recruited from two CHRPCs in Europe: the INSURE program from the Käpylä Rehabilitation Centre, Helsinki, Finland, and the other from the Reade Centre for Rehabilitation, Amsterdam, the Netherlands. The inclusion criteria in Study III were (1) voluntary agreement to participate; (2) underwent systematic neuropsychological rehabilitative treatments in a CHRP; (3) residing in their respective communities (i.e. not requiring custodial care); (4) resumed working in a capacity commensurate with their postrehabilitative abilities following a CHRP for a minimum of six months after discharge; and (5) experiencing no functionally incapacitating medical or psychological problems following a CHRP for a minimum of six months after discharge.

A total of 57 consecutively admitted participants from the CHRPCs (35 Finnish and 22 Dutch patients) were invited to participate in the study. Of the participants, seven did not meet all the inclusion criteria, three were unwilling to participate, and two could not be reached. Demographic and injury-related data was obtained from hospital files. The characteristics of the 45 eligible patients (27 Finnish, 18 Dutch), comprising 34 men and 11 women, with a moderate to severe TBI (proportion of PTA, 80% over a week) are shown in Table 4. Their mean age was 30.1 years (SD ± 10.3 years; range: 15.0–52.0 years). The mean time from injury to evaluation was 9.7 years (SD ± 5.5 years; range: 4.0–36.0 years). At the time of the evaluation, the mean time that patients had been working after the CHRP was 4.7 years (SD ± 2.3 years; range: 0.7–8.0 years).

Patients’ premorbid personal, vocational, and social adjustments were also estimated. Premorbid estimates of adjustment were based on clinical team
consensus among members of the respective teams along a 5-point rating scale (consistently good, mostly satisfactory, occasionally/slightly problematic, considerably problematic, and consistently troubled) by using hospital files and clinical interviews of the patients and their significant others. The preinjury estimated personal, vocational and social adjustments were within the ‘consistently good’ or the ‘mostly satisfactory’ range for 76–85% of patients (Table 4). Patients’ level of intellectual functioning at the time of their attendance to the CHRP was estimated from neuropsychological assessment files on the basis of neuropsychology staff consensus as follows: borderline intelligence quotient (IQ), range 65–80; average IQ, range 80–110; high average IQ, range 110–120; and superior IQ, range >120. The IQ levels of the patients within the average range were 44%, and 40% of patients had IQ levels above the average range (Table 4). Neuropsychologic sequelae of the patients consisted of various combinations of problems common in TBI, including tendency to be fatigued, slowness of information processing, disorders of attention and concentration, disorders of learning and memory, disturbances in executive skills, difficulties in modulating affective states, and disorders of language communication. The patients were independent in their daily life activities and had only slight physical disabilities.
Table 4. Demographic and injury-related characteristics (n = 45).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% or Mean (SD) [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>75.6</td>
</tr>
<tr>
<td>Age at injury, years</td>
<td>30.1 (10.3) [15.0–52.0]</td>
</tr>
<tr>
<td>Time between injury and evaluation, years</td>
<td>9.7 (5.5) [4.0–36.0]</td>
</tr>
<tr>
<td>Time at work postdischarge, years</td>
<td>4.7 (2.3) [0.7–8.0]</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>13.3</td>
</tr>
<tr>
<td>Upper secondary</td>
<td>75.6</td>
</tr>
<tr>
<td>Higher</td>
<td>11.1</td>
</tr>
<tr>
<td>Injury mechanism</td>
<td></td>
</tr>
<tr>
<td>Motor vehicle collision</td>
<td>31.1</td>
</tr>
<tr>
<td>Bicycle collision</td>
<td>31.1</td>
</tr>
<tr>
<td>Pedestrian-auto collision</td>
<td>8.9</td>
</tr>
<tr>
<td>Assault</td>
<td>6.7</td>
</tr>
<tr>
<td>Other, fall, hit by an object</td>
<td>17.8</td>
</tr>
<tr>
<td>Unknown</td>
<td>4.4</td>
</tr>
<tr>
<td>Posttraumatic amnesia</td>
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</tr>
<tr>
<td>&lt;24 hours</td>
<td>4.4</td>
</tr>
<tr>
<td>1–7 days</td>
<td>8.9</td>
</tr>
<tr>
<td>1–4 weeks</td>
<td>28.9</td>
</tr>
<tr>
<td>&gt;4 weeks</td>
<td>51.1</td>
</tr>
<tr>
<td>Not assessable or unknown</td>
<td>6.7</td>
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<tr>
<td>CT/MRI findings, n</td>
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<tr>
<td>Contusion and/or intracranial hematoma</td>
<td>84.4</td>
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<tr>
<td>Diffuse axonal injury</td>
<td>26.7</td>
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<tr>
<td>Signs of severe intracranial pressure</td>
<td>37.8</td>
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<tr>
<td>None</td>
<td>4.4</td>
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<tr>
<td>Estimated preinjury adjustment</td>
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<tr>
<td>Personal</td>
<td>Consistently good</td>
</tr>
<tr>
<td></td>
<td>Mostly satisfactory</td>
</tr>
<tr>
<td></td>
<td>Slightly problematic</td>
</tr>
<tr>
<td></td>
<td>Considerably problematic</td>
</tr>
<tr>
<td>Vocational</td>
<td>Consistently good</td>
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<td>Mostly satisfactory</td>
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<td>Slightly problematic</td>
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<td>Considerably problematic</td>
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<tr>
<td>Social</td>
<td>Consistently good</td>
</tr>
<tr>
<td></td>
<td>Mostly satisfactory</td>
</tr>
<tr>
<td></td>
<td>Slightly problematic</td>
</tr>
<tr>
<td></td>
<td>Considerably problematic</td>
</tr>
<tr>
<td>Level of intellectual functioning</td>
<td></td>
</tr>
<tr>
<td>Within the borderline range of 65–80</td>
<td>2.2</td>
</tr>
<tr>
<td>Within the average range of 80–110</td>
<td>44.4</td>
</tr>
<tr>
<td>Within the high average range of 110–120</td>
<td>40.0</td>
</tr>
<tr>
<td>Within the superior range of &gt;120</td>
<td>13.3</td>
</tr>
</tbody>
</table>
The multidisciplinary staff of both the CHRPs includes neuropsychologists, physical therapists, and social workers or vocational therapists. Moreover, the staff of the Finnish program INSURE contains professionals in neurology, speech and language therapy, occupational therapy, art therapy and nursing. The patient-staff ratio in the Finnish program is 1:1.5, and in the Dutch program 1:1. The total number of treatment hours is 150–160 in the Finnish inpatient program and 220–230 in the Dutch day treatment program.

### 3.3.2 Measures and Procedures

**Objective outcome measure.** The staff neuropsychologists interviewed in detail the patients by telephone to get adequate descriptions of their actual preinjury occupation and the postrehabilitation type or scope of their productive activities. Attained types of work were transposed along a 10-point scale by an experienced neuropsychologist who was not involved in the patients’ care (Appendix B). For the purpose of statistical analyses, three categories of the levels of work attained postdischarge were used: sheltered workshop or volunteer work (levels 1–4), subsidized work (levels 5–6), and competitive work (levels 7–10).

**Subjective outcome measure.** To assess patients’ subjective self-appraisal of postrehabilitation outcomes, an evaluation instrument shown in Table 5 (Ben-Yishay et al., 1987; Ben-Yishay & Daniels-Zide, 2000) was used. According to Ben-Yishay and Daniels-Zide (2000), extensive clinical experience has shown that the six items of the self-rating instrument tend to elicit clinically different, but meaningful information. The self-evaluative rating scale with instructions was mailed to the patients for them to rate themselves in six areas: effort during rehabilitation, meaning in life, productivity, acceptance, social life, and intimate relationships, which was defined as closely acquainted or familiar. Patients were asked to rate the six areas along a 10-point scale from the best (a rating of 10) to the worst (a rating of 1) in a 2-week period in order to give them time to figure out their ratings. After that patients were phoned and inquired the results of their self-ratings. If needed, the precise clinical meaning of the questions as intended in the study were clarified to the patients. Attention was especially paid to the clarification of the concept ‘intimate relationships’, referring to the self-appraised ability to establish close relationships in general, not only in the sense of a relationship to a partner.
### Table 5.  Self-rating in six areas of wellness following rehabilitation (Ben-Yishay & Daniels-Zide 2000).

<table>
<thead>
<tr>
<th>Area</th>
<th>Rating scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>My effort during rehabilitation to overcome the difficulties that were caused by my brain injury has been:</td>
<td>Nothing special</td>
</tr>
<tr>
<td>Although different from what it was before my brain injury, my present life is:</td>
<td>Just tolerable</td>
</tr>
<tr>
<td>Since rehabilitation, I have been leading a/an:</td>
<td>Unproductive life</td>
</tr>
<tr>
<td>After rehabilitation I feel that I am:</td>
<td>Still not at peace with myself</td>
</tr>
<tr>
<td>My social life following rehabilitation is:</td>
<td>Most unsatisfactory</td>
</tr>
<tr>
<td>My ability to establish intimate relationships is:</td>
<td>Very poor</td>
</tr>
</tbody>
</table>

#### 3.3.3 STATISTICAL ANALYSES

Descriptive statistics were used to characterize the participants. The values of the variables on the self-appraisal scale are presented as means, medians, quartiles [lower quartile (Q1), upper quartile (Q3)], and minimums and maximums. Because of non-normal distribution and the small number of participants, IQ and the subjective ratings were divided into three categories, and Kendall’s Taus were calculated to assess the relationship between the three-category IQ (65–110, 110–120, over 120) and the subjective rating, which were also divided into three categories (cut-off points for categories vary depending on the variable). Univariate ordinal regression was used to assess the association between the six areas of self-appraisal as well as the sum of the self-appraisals and categorized level of work attained postdischarge. Three categories for the levels of work attained postdischarge were formed from the 10-point scale as follows: 1 to 4 (sheltered workshop or volunteer work), 5 to 6 (subsidized work) and 7 to 10 (competitive work), and a test of parallel lines was used for each model to make sure that the proportional odds assumption holds.

To examine whether skewness of the distribution of the self-appraisals had an effect on the results, associations between the three-category levels of work and the subjective self-appraisal of the areas of wellness following rehabilitation were verified by dividing each area of the subjective self-appraisal into two or three categories and using these categorical variables instead of numerical ones in the ordinal regression models as an explanatory variable. The SPSS software package version 22 (Chicago, IL, USA) was used for the statistical analysis.
4 RESULTS

4.1 OUTCOME OF THE INSURE PROGRAM FOR TBI (STUDY I)

The patient group receiving rehabilitation treatment and the control group did not differ significantly from each other on any of the demographic or injury-related matching variables (see Table 1). The consistency of the classification of patients into the productive and nonproductive categories by the two independent raters was perfect. As seen in Table 6, at the end of the 2-year follow-up, 89% of patients in the treatment group and 55% of controls were productive. The outcome of the treatment group was significantly better than that of the control group (OR 6.96; 95% CI: 1.26–38.44; P = 0.02).

Table 6. Number of productive and nonproductive patients in the Treatment and Control groups at outcome evaluation.

<table>
<thead>
<tr>
<th>Status</th>
<th>Treatment group (n = 19), n (%)</th>
<th>Control group (n = 20), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Productive</td>
<td>17 (89)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Nonproductive</td>
<td>2 (11)</td>
<td>9 (45)</td>
</tr>
</tbody>
</table>

NOTE. OR = 6.96; 95% CI, 1.26–38.44, $\chi^2$ test = 5.718, df = 1, $P = 0.017$.

Table 7 shows the numbers of patients classified according to the type of productive activity before the INSURE program and at follow-up for treated and control groups. The productivity status of the treated patients clearly improved during this time interval. Two treated patients who were unproductive at the time of evaluation were looking for supported work-trial places. At the time of follow-up, seven control patients were in gainful full-time work, one was in gainful part-time work, and three were studying. Three of them reported significant difficulties related to working or studying after TBI, and two reported that their jobs were less demanding than before TBI. The proportion of patients engaged in gainful work at follow-up was bigger in the control group than in the treatment group, but the difference was not statistically significant ($\chi^2$ test = 1.64, $P = 0.20$).

The potential confounding variables used in the logistic regression analysis were age at injury, sex, education, chronicity (time from injury to outcome evaluation), injury severity (GCS score), and preinjury employment status. Of these variables, only the preinjury employment status was significantly associated with productivity (OR 7.43; 95% CI: 1.12–49.24; $P = 0.04$). Unemployed patients at the time of injury were more likely than others to
be unproductive at follow-up (67% vs. 21%). The treatment variable and all of the potential confounding variables were entered simultaneously into the logistic regression model with productivity status as the dependent variable. However, some of the regression coefficients in this model were poorly estimated because of both high intercorrelations of some independent variables (age at injury and education, $r = 0.55$) and a small number of participants in the ‘unemployed’ category of preinjury employment status ($n = 6$). Including either the combination of ‘age at injury’ and ‘education’ or the combination of ‘treatment’ and ‘employment status’ as independent variables in the model produced a huge increase in standard errors of regression coefficients of these variables. For better fit of the model, the variables of education and preinjury employment status were excluded from the analysis.

A logistic regression analysis (Table 8) showed that the rehabilitation program was significantly predictive of a productive status at follow-up when adjusted for the remaining independent variables (OR 7.19; 95% CI: 1.23–42.20; $P = 0.03$). Dropout of the independent variables from the model was of no importance from the viewpoint of interpretation of the results, which we can conclude based on additional analysis. In the model in which age at injury was replaced with education, the association between rehabilitation program and productivity status was very similar (OR 8.39; 95% CI: 1.54–52.54; $P = 0.02$). The association between treatment and productivity status was not confounded by preinjury employment status because the association was obvious both among patients who were employed or studying at the time of injury (OR 11.19; 95% CI: 0.89–140.99; $P = 0.06$) and among those who were unemployed. Since there were only six patients in the latter group, statistical testing was not applicable. Nevertheless, the two patients who were productive were in the treatment group.

Table 7. Type of productive activity before treatment for the Treatment group patients and at outcome evaluation for the Treatment and Control group patients.

<table>
<thead>
<tr>
<th>Type of productive activity</th>
<th>Pretreatment Treatment patients ($n = 19$)</th>
<th>2-year follow-up Treatment patients ($n = 19$)</th>
<th>Control patients ($n = 20$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gainful work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>0</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Part-time</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Education / student</td>
<td>0</td>
<td>4$^a$</td>
<td>3</td>
</tr>
<tr>
<td>Work trial</td>
<td>0</td>
<td>3$^b$</td>
<td>0</td>
</tr>
<tr>
<td>Productive but nongainful work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Part-time</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Volunteer work (organized and routine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No productive activity$^c$</td>
<td>18</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

$^a$ Six of the patients who were at school or on a work trial were aiming at gainful part-time work and one patient at productive but nongainful part-time work.

$^b$ One patient was an independent homemaker and taking care of a single-parent family.

$^c$ No working, studying, or participation in organized and routine volunteer work.
Table 8. Productivity status\textsuperscript{a} explained by treatment and other variables using logistic regression analysis (n = 39).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>OR (95% CI)</th>
<th>P\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment\textsuperscript{b}</td>
<td>1.97</td>
<td>0.90</td>
<td>7.19 (1.23−42.20)</td>
<td>0.029</td>
</tr>
<tr>
<td>Sex\textsuperscript{c}</td>
<td>0.11</td>
<td>1.09</td>
<td>1.11 (0.13−9.35)</td>
<td>0.921</td>
</tr>
<tr>
<td>Age at injury, years</td>
<td>−0.027</td>
<td>0.039</td>
<td>0.97 (0.90−1.05)</td>
<td>0.481</td>
</tr>
<tr>
<td>Chronicity, months</td>
<td>−0.021</td>
<td>0.020</td>
<td>0.98 (0.94−1.02)</td>
<td>0.296</td>
</tr>
<tr>
<td>GCS score</td>
<td>0.14</td>
<td>0.17</td>
<td>1.15 (0.82−1.60)</td>
<td>0.416</td>
</tr>
<tr>
<td>Constant</td>
<td>0.81</td>
<td>2.27</td>
<td>2.25 (0.72−7.21)</td>
<td>0.721</td>
</tr>
</tbody>
</table>

NOTE. Categoric variables were coded as 0 and 1 as follows:
\textsuperscript{a} Productive = 1, nonproductive = 0
\textsuperscript{b} INSURE = 1, control = 0
\textsuperscript{c} Men = 1, women = 0.
Abbreviation: SE, standard error.
\textsuperscript{d} Wald test.

4.2 RELATIONSHIP BETWEEN COGNITIVE AND MOTOR PERFORMANCE IN TBI (STUDY II)

Neuropsychological and motor performance test results of the patients are shown in Table 9. In order to measure the static balance, the patients were asked to stand on the right and left leg in turn; almost half of them were unable to maintain their balance on one leg (44% on the right, 50% on the left leg) for 60 s. In the slow phase of the rhythm coordination test, 41% of the patients had difficulty in starting and/or maintaining the given rhythm, and 62% had difficulty with coordination during the fast phase.

Correlations between the continuous neuropsychological and motor performance test results are shown in Table 10. The highest rank correlations were between the time for both TM tests and the performance time for running a figure-of-8 ($r_s = 0.57$). Moreover, the scores on the Digit Symbol test correlated inversely with the latter ($r_s = 0.52$; 95% CI: 0.74–0.19). The original values behind these highest rank correlations are shown in scatter-plots in Figure 2. Other correlations between these variables were only weak or moderate ($< 0.35$).
Table 9. Results of neuropsychological and motor performance tests.

<table>
<thead>
<tr>
<th>Test</th>
<th>Maximum score or retaining %</th>
<th>Frequencies</th>
<th>Mean (SD) [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropsychological tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERAD battery (n = 34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency (naming animals)</td>
<td>−/&lt; 15</td>
<td>29 / 5</td>
<td></td>
</tr>
<tr>
<td>15-item Boston Naming Test</td>
<td>15/&lt; 11</td>
<td>32 / 2</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening score</td>
<td>30/&lt; 25</td>
<td>34/0</td>
<td>27.7 (1.7) [25–30]</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word list learning</td>
<td>30/−</td>
<td></td>
<td>19.6 (3.4) [13–26]</td>
</tr>
<tr>
<td>Word list recall</td>
<td>10/–100/&lt; 80</td>
<td>26 / 8</td>
<td></td>
</tr>
<tr>
<td>Word list recognition</td>
<td>20/–100/&lt; 80</td>
<td>33 / 1</td>
<td></td>
</tr>
<tr>
<td>Constructional praxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drawing (a clock)</td>
<td>6/&lt; 5</td>
<td>31 / 3</td>
<td></td>
</tr>
<tr>
<td>Copy (figures)</td>
<td>11/&lt;</td>
<td></td>
<td>10.7 (0.9) [7–11]</td>
</tr>
<tr>
<td>Recall of constructional praxis</td>
<td>11/–100/&lt; 60</td>
<td>30 / 4</td>
<td></td>
</tr>
<tr>
<td>Trial Making Test, s</td>
<td></td>
<td>50.5 (24.1) [23–145]</td>
<td></td>
</tr>
<tr>
<td>WAIS-R (subtest) (n = 34)</td>
<td></td>
<td>125.8 (60.8) [54–310]</td>
<td></td>
</tr>
<tr>
<td>Digit symbol</td>
<td></td>
<td>41.9 (11.1) [25–77]</td>
<td></td>
</tr>
<tr>
<td>LNI: motor functions and acoustico-motor organization (subtests) (n = 33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor functions of hands</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple forms of praxis</td>
<td>20 / 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex forms of praxis</td>
<td>29 / 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dynamic organization</td>
<td>16 / 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speech regulation of motor act</td>
<td>30 / 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acoustico-motor organization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perception of rhythmic structures</td>
<td>27 / 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproduction of rhythmic structures</td>
<td>17 / 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Motor performance tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 km Walk Test (n = 34), m:s</td>
<td>18:29 (2:09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agility (n = 34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Running figure-of-8, s</td>
<td>8.4 (2.1) [6.2–15.6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dynamic balance (n = 34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tandem walking forwards, s</td>
<td>14.9 (4.3) [9.3–28.5]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tandem walking backwards, s</td>
<td>17.6 (6.3) [10.0–37.2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Static balance (n = 34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balance on right leg, &lt; 60 s/60 s</td>
<td>15 / 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balance on left leg, &lt; 60 s/60 s</td>
<td>17 / 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhythm coordination (n = 34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow rhythm, 0–6 points/7–8 points</td>
<td>14 / 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast rhythm, 0–6 points/7–8 points</td>
<td>21 / 13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; MMSE, Mini Mental State Examination; WAIS-R, Wechsler Adult Intelligence Scale, Revised; LNI, Luria’s Neuropsychological Investigation.
Figure 2. Scatter-plots between Trail Making and Wechsler Adult Intelligence Scale Revised (WAIS-R) Digit symbol tests and running a figure-of-8 test.

Table 10. Correlations between neuropsychological and motor performance test results (Spearman’s partial rank correlation coefficients).

<table>
<thead>
<tr>
<th>Test</th>
<th>Tandem walking forwards, s r_s (95% CI)</th>
<th>Tandem walking backwards, s r_s (95% CI)</th>
<th>Running figure-of-8, s r_s (95% CI)</th>
<th>Rhythm test, score r_s (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERAD, score (n = 33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td>0.15&lt;sup&gt;a&lt;/sup&gt; (-23 to 0.49)</td>
<td>0.19 (-0.19 to 0.52)</td>
<td>0.11 (-0.27 to 0.46)</td>
<td>-12 (-0.46 to 0.26)</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word list learning</td>
<td>-17 (-0.51 to 0.21)</td>
<td>-0.31 (-0.61 to 0.07)</td>
<td>-0.33 (-0.62 to 0.04)</td>
<td>-0.05 (-0.41 to 0.33)</td>
</tr>
<tr>
<td>Trail Making Test, s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial A (n = 33)</td>
<td>0.34 (-0.03 to 0.63)</td>
<td>0.23 (-0.15 to 0.55)</td>
<td>0.57 (0.26 to 0.78)</td>
<td>-0.23 (-0.55 to 0.15)</td>
</tr>
<tr>
<td>Trial B (n = 32)</td>
<td>0.33 (-0.05 to 0.63)</td>
<td>0.26 (-0.13 to 0.58)</td>
<td>0.57 (0.25 to 0.78)</td>
<td>-0.32 (-0.62 to 0.06)</td>
</tr>
<tr>
<td>WAIS-R, subtest, score (n=33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit symbol</td>
<td>-0.37 (-0.65 to 0.00)</td>
<td>-0.18 (-0.51 to 0.20)</td>
<td>-0.52 (-0.74 to -0.19)</td>
<td>0.01 (-0.36 to 0.37)</td>
</tr>
</tbody>
</table>

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; CI, confidence interval; MMSE, Mini Mental State Examination; WAIS-R, Wechsler Adult Intelligence Scale Revised.

<sup>a</sup> Spearman partial rank correlation coefficient adjusted for age, length of education, posttraumatic amnesia and time from injury.
The distributions of the motor performance test results in subcategories of categorized neuropsychological tests are shown in Figure 3, and the adjusted between-group differences in Table 11. Patients with normal results in verbal fluency achieved 26% faster mean performance time in tandem walking forwards (GMR 0.74; 95% CI: 0.55–1.00) and running a figure-of-eight (GMR 0.74; 95% CI: 0.61–0.89) than those with abnormal fluency. Patients with a normal result in the reproduction of rhythmic structures produced, on average, 20% and 23% better performance times in tandem walking forwards (GMR 0.80; 95% CI: 0.65–1.00) and tandem walking backwards (GMR 0.77; 95% CI: 0.59–1.00), respectively. Motor functions of the hands (simple and complex forms of praxis) correlated significantly with all motor tests.

Table 11. Differences in motor performance tests between normal and pathological values in neuropsychological tests.

<table>
<thead>
<tr>
<th>Test</th>
<th>Tandem walking forwards, s Mean (SD)</th>
<th>Tandem walking backwards, s Mean (SD)</th>
<th>Running figure-of-eight, s Mean (SD)</th>
<th>Rhythm test, score Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CERAD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Verbal fluency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n = 28)</td>
<td>14.3 (4.2)</td>
<td>17.1 (6.7)</td>
<td>7.9 (1.5)</td>
<td>10.8 (5.2)</td>
</tr>
<tr>
<td>Pathological (n = 5)</td>
<td>18.8 (3.1)</td>
<td>20.6 (4.2)</td>
<td>11.3 (2.9)</td>
<td>7.6 (5.4)</td>
</tr>
<tr>
<td>Geometric mean ratio&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.74 (0.55–1.00)</td>
<td>0.83 (0.57–1.20)</td>
<td>0.74 (0.61–0.89)</td>
<td>Mean diff.&lt;sup&gt;a&lt;/sup&gt; 3.3 (–2.5–9.2)</td>
</tr>
<tr>
<td><strong>Constructional praxis: copy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n = 27)</td>
<td>14.3 (4.3)</td>
<td>16.7 (6.4)</td>
<td>8.0 (1.5)</td>
<td>10.7 (5.4)</td>
</tr>
<tr>
<td>Pathological (n = 6)</td>
<td>17.8 (3.1)</td>
<td>21.7 (5.3)</td>
<td>10.3 (3.5)</td>
<td>8.5 (5.0)</td>
</tr>
<tr>
<td>Geometric mean ratio&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.77 (0.58–1.03)</td>
<td>0.75 (0.53–1.06)</td>
<td>0.82 (0.67–1.01)</td>
<td>Mean diff.&lt;sup&gt;a&lt;/sup&gt; 2.8 (–2.9–8.5)</td>
</tr>
<tr>
<td><strong>LNI: motor functions and acoustico-motor organization (subtests)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Simple and complex form of praxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n = 11)</td>
<td>11.9 (2.4)</td>
<td>13.4 (3.2)</td>
<td>7.3 (1.0)</td>
<td>13.6 (4.1)</td>
</tr>
<tr>
<td>Pathological (n = 21)</td>
<td>16.3 (4.4)</td>
<td>19.8 (6.8)</td>
<td>9.0 (2.4)</td>
<td>8.5 (5.2)</td>
</tr>
<tr>
<td>Geometric mean ratio&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.74 (0.60–0.90)</td>
<td>0.69 (0.54–0.88)</td>
<td>0.81 (0.70–0.95)</td>
<td>Mean diff.&lt;sup&gt;a&lt;/sup&gt; 5.9 (2.0–9.7)</td>
</tr>
<tr>
<td><strong>Reproduction of rhythmic structures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n = 16)</td>
<td>13.1 (2.9)</td>
<td>14.9 (3.9)</td>
<td>7.8 (1.2)</td>
<td>11.2 (5.2)</td>
</tr>
<tr>
<td>Pathological (n = 16)</td>
<td>16.6 (4.9)</td>
<td>20.3 (7.6)</td>
<td>9.0 (2.8)</td>
<td>9.4 (5.6)</td>
</tr>
<tr>
<td>Geometric mean ratio&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.80 (0.65–1.00)</td>
<td>0.77 (0.59–1.00)</td>
<td>0.93 (0.79–1.10)</td>
<td>Mean diff.&lt;sup&gt;a&lt;/sup&gt; 2.6 (–1.7–7.0)</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.

<sup>a</sup> Geometric mean ratio (95% confidence interval (CI)) or mean difference (95% CI) between categories of neuropsychological tests (normal vs. pathological) are estimated by analysis of covariance and they are adjusted for confounders (age, length of education, posttraumatic amnesia, and time from injury). The difference is expressed as geometric mean ratio for log-transformed dependent variables and as mean difference for dependent variables without transformation.
4.3 RELATIONSHIP BETWEEN OBJECTIVE AND SUBJECTIVE OUTCOMES OF COMPREHENSIVE-HOLISTIC NEUROREHABILITATION FOR PATIENTS WITH TBI (STUDY III)

Of the patients 67% attained competitive employment, 54% in part-time and 13% in a full-time capacity. A further 20% attained subsidized and 11% volunteer or sheltered workshop work ability. Figure 4 shows the number of patients classified according to the level of work competence achieved after rehabilitation.

Results of the self-appraisals in six areas of subjective outcomes and wellness following rehabilitation are presented in Table 12. The median for the different areas of self-ratings was between eight and nine out of ten. The lowest ratings were related to the ability to establish intimate relationships. The three-category IQ was not significantly related to any of the three-category subjective areas of self-appraisal.
Figure 4. Level of work competence attained after rehabilitation at the time of evaluation for participants.

Table 12. Results of self-appraisals for participants (n = 45).

<table>
<thead>
<tr>
<th>Six areas of self-appraisal</th>
<th>Mean</th>
<th>Median</th>
<th>Q1</th>
<th>Q3</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effort during rehabilitation</td>
<td>8.6</td>
<td>9.0</td>
<td>8.0</td>
<td>9.0</td>
<td>5.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Meaningfulness in life</td>
<td>8.1</td>
<td>8.0</td>
<td>7.0</td>
<td>9.0</td>
<td>4.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Productivity in life</td>
<td>8.3</td>
<td>8.0</td>
<td>8.0</td>
<td>9.0</td>
<td>4.0</td>
<td>10.0</td>
</tr>
<tr>
<td>At peace with oneself</td>
<td>7.9</td>
<td>8.0</td>
<td>7.0</td>
<td>9.0</td>
<td>4.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Satisfaction with social life</td>
<td>7.7</td>
<td>8.0</td>
<td>7.0</td>
<td>9.0</td>
<td>3.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Ability to establish intimate relations</td>
<td>7.4</td>
<td>8.0</td>
<td>7.0</td>
<td>8.0</td>
<td>3.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Sum of self-ratings</td>
<td>48.0</td>
<td>49.0</td>
<td>45.0</td>
<td>51.0</td>
<td>33.0</td>
<td>58.0</td>
</tr>
</tbody>
</table>

Abbreviations: Q1, lower quartile; Q3, upper quartile.

Associations between the subjective self-appraisals and the three-category level of work are shown in Table 13. The subjective self-appraisal for the ability to establish intimate relationships had a significant association with the levels of work (OR 1.79; 95% CI: 1.20–2.68; P = 0.005). Otherwise, no significant associations between areas of subjective ratings and levels of work attained by participants were found. Skewness of the distribution of self-appraisals did not have an effect on the results.
Table 13. Three-category level of working attained postdischarge explained by one area of self-appraisal at a time using univariable ordinal regression analysis.

<table>
<thead>
<tr>
<th>Six areas of self-appraisal</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effort during rehabilitation</td>
<td>1.40</td>
<td>0.83−2.36</td>
<td>0.21</td>
</tr>
<tr>
<td>Meaningfulness in life</td>
<td>1.22</td>
<td>0.80−1.86</td>
<td>0.37</td>
</tr>
<tr>
<td>Productivity in life</td>
<td>0.76</td>
<td>0.47−1.23</td>
<td>0.26</td>
</tr>
<tr>
<td>At peace with oneself</td>
<td>1.28</td>
<td>0.88−1.85</td>
<td>0.20</td>
</tr>
<tr>
<td>Satisfaction with social life</td>
<td>0.98</td>
<td>0.66−1.46</td>
<td>0.93</td>
</tr>
<tr>
<td>Ability to establish intimate</td>
<td>1.79</td>
<td>1.20−2.68</td>
<td>0.005</td>
</tr>
<tr>
<td>relationships</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum of self-ratings</td>
<td>1.08</td>
<td>0.97−1.21</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; CI, confidence interval.
The studies herein investigated the psychosocial outcomes of an application of a comprehensive-holistic rehabilitation program (CHRP) (Study I), the relationship between the objective outcomes and their subjective self-appraisal in adults with postacute TBI (Study III), and the relationship between cognitive and motor functions for benefits in multidisciplinary neurorehabilitation after TBI (Study II). The results of Study I showed that the CHRP applied was significantly predictive of the productive status at follow-up compared with conventional clinical care and rehabilitation. Moreover, the findings of Study III indicated that the levels of work obtained after CHRP were not associated with the areas of subjective self-appraisals other than the ability to establish intimate relationships, suggesting that community functioning and related satisfaction are distinct aspects of the participants’ experience that both need to be considered in the evaluation of rehabilitation to enhance subjective well-being after TBI. Overall, the patients were found to be largely satisfied with the areas of wellness after CHRPs. Explorative Study II, which analyzed the relationship between cognitive and motor functions in postacute TBI, found associations of measures of information processing, attention, and executive functioning with agility and dynamic balance. This supports earlier proposals of these relationships (Cantin et al., 2007; Geurts et al., 1999; Sosnoff et al., 2008) and suggests important clinical implications for benefiting from these associations in multidisciplinary rehabilitation after TBI. In the following sections, three topics relevant to the studies will be discussed in more detail: (1) the comprehensive-holistic rehabilitation approach and outcomes in TBI, (2) the clinical relevance of interrelatedness of cognitive and motor functions regarding multidisciplinary comprehensive rehabilitation in TBI, and (3) the subjective appraisals of objective outcomes after comprehensive-holistic rehabilitation for TBI.

5.1 COMPREHENSIVE-HOLISTIC REHABILITATION APPROACH AND OUTCOMES IN TBI

TBI has been considered one of the most challenging areas in modern rehabilitation medicine (Borg et al., 2011; Cnossen et al., 2017). The complexity is due to the nature of TBI as a heterogeneous and lifelong disorder with a myriad of diverse consequences and changing needs over time that impact multiple aspects of daily functioning, social relationships, community integration, and QoL (Corrigan et
al., 2013; CDC, 2017; Katz et al., 2013; Maas et al., 2017). To meet the varying needs of TBI patients, theoretically sound, evidence-based, cost-effective, and clinically applicable rehabilitation models are required to promote recovery and to achieve desired outcomes such as reducing disability and improving health, functioning, independence, social reintegration, and QoL, and to address the longer-term complications (Coetzer et al., 2018; Maas et al., 2017; Ottenbacher et al., 2012). However, multiple factors that comprise a complex interplay between various premorbid characteristics, injury-related factors, postinjury impairments, and environmental factors have been found to be related to outcome following TBI, which makes outcome prediction challenging (Holland & Schmidt, 2015; Humphreys et al., 2013; Jordan, 2007; Luria, 1948/1963; Nightingale, Soo, & Tate, 2007; Ownsworth & Clare, 2006; Ponsford et al., 2008; Ponsford et al., 2016; Prigatano, 1999; Rassovsky et al., 2015; Santarsieri, Kumar, Kochanek, Berga, & Wagner, 2015; Schönberger et al., 2011; Sela-Kaufman et al., 2013; van Velzen et al., 2009; Zasler, 1997).

Considering the marked diversity, complexity, and interaction of consequences after TBI in cognitive, emotional, behavioral, physical, personal, and environmental domains it has become evident that comprehensive rehabilitation of persons with TBI requires multiple healthcare professionals and is best addressed by multidisciplinary team approaches (Turner-Stokes, 2008; Körner, 2010; Maas et al., 2017; Wertheimer et al., 2008). Moreover, different forms of rehabilitation are needed for different subgroups of TBI patients and at different phases over the course of recovery to optimize outcomes. Trying to identify the subgroups most likely to benefit from different kinds of therapies would allow more judicious allocation of resources and improve outcomes (Dikmen et al., 1995; Maas et al., 2017; NIH Consensus Conference, 1999).

Standards of care, rehabilitation interventions, and rehabilitation research for TBI patients have been developed over the last three decades, yet robust evidence for promoting effective practices is scarce, and evidence-based guidelines do not exist for most rehabilitation interventions (Borg et al., 2011; Fronter et al., 2017; Malec, 2013, Maas et al., 2017; Ottenbacher et al., 2012). Moreover, recommended practices have been found to be inconsistently implemented between centers and often do not sufficiently address the diversity of consequences related to TBI (Cnossen et al., 2017; Maas et al., 2017). In addition, research on TBI rehabilitation is difficult since it addresses methodological challenges and obstacles that do not occur in typical clinical drug trials (High, Boake, & Lehmkuhl, 1995; Frontera et al., 2017; Maas et al., 2017; NIH, 1999). TBI rehabilitation is also such an individualized and long-term process that studies exploring it do not necessarily give rise to general conclusions (Turner-Stokes, Pick, Nair, Disler, & Wade, 2015).
It has become increasingly evident that outcome assessment of TBI should be multidimensional to show treatment effects (Honan et al., 2019; Kean & Malec, 2014; Maas et al., 2017; Wilde et al., 2010). Moreover, viewing outcomes after TBI in conventional ways using merely objective metrics does injustice to the values and goals of the patient served (e.g. Brown & Gordon, 2004; Evans & Ruff, 1992; Prigatano, 1999). The conventional route has also been criticized for missing the bigger picture of rehabilitation and to depriving professionals of a meaningful way to determine if and when the person with brain injury has reached full rehabilitation potential (Ben-Yishay & Daniels-Zide, 2000). An emerging area in TBI research is to evaluate outcomes of interventions in order to capture the patient-reported outcome, i.e. determining whether the activities targeted by rehabilitation are those most valued by patients, contribute strongly to their QoL and subjective well-being (Bullinger, 2002; Dijkers, 2004; von Steinbuechel et al., 2012).

The findings of Study I showed that the proportion of productive patients was significantly higher in the CHRP group than in the matched control group receiving conventional clinical care and rehabilitation. The likelihood of being productive was greater among patients who were employed or studying at the time of injury, which is in line with previous findings (Gollaher et al., 1998; Ip, Dornan, & Schentag, 1995; Ponsford et al., 1995; Sander et al., 1996). The rate of productivity was quite consistent with that reported in earlier studies on the efficacy of CHRPs in postacute patients. Ben-Yishay with colleagues (1987) reported that 84% of the 94 previously nonproductive patients with chronic TBI, and Christensen with colleagues (1992) that over 70% of the 46 patients with brain injury engaged in productive activities after CHRP. Klonoff and colleagues (2001) reported that 83.5% of 164 patients with brain injury were productive in some capacity up to 11 years postdischarge from CHRP. None of these studies included a nontreatment control group. Prigatano and colleagues (1984) using a control group reported 50% productivity for 18 patients with TBI in a CHRP group at follow-up compared with 36% of 17 controls receiving traditional rehabilitation. This study was replicated (Prigatano et al., 1994) in a group of 38 TBI patients with 38 controls in a different rehabilitation setting. When part-time and volunteer work were taken into account, 77% of treated patients were productive compared with 47% of controls.

Productivity was strongly polarized in the control group of Study I. Nine of the 20 control patients were completely unproductive, whereas 11 were involved in gainful work or studying. An explanation for this finding could be that the control patients were more productive than the patients in the treatment group more than two years before the outcome evaluation, at the beginning of the treatment program. The two groups were similar with respect to background
characteristics, injury severity, and time from injury to outcome evaluation, but the control patients were not selected to match patients in the treatment group with respect to their pretreatment productivity, although the groups were matched regarding employment status before injury.

An additional question related to return to work (RTW) activities concerned strategies for returning to work or productive activity. An essential element in the INSURE program and other CHRPs is supported vocational interventions. Individually tailored placements and supported work trials help patients find productive activities that fit their interests and abilities after TBI (NIH Consensus Conference 1999; Wehman et al., 1995, 1999, 2003). Effective interventions for RTW activities as a psychosocial outcome for individuals with TBI have been shown to include a comprehensive approach, both medical and psychosocial aspects with combinations of vocational rehabilitation with supported employment, coaching and education, and skills training (for review, see Donker-Cools, Daams, Wind, & Monique, 2016). The most effective interventions have reported to include a tailored approach, early intervention, involvement of both the patient and employer, work accommodations, practicing at work, and training of interpersonal, work-related and coping skills with emotional support (Donker-Cools et al., 2016). However, in conventional clinical care and rehabilitation of TBI such interventions are generally used in a less systematic way, if at all.

Participation in work-related activities has been shown to have a consistent relationship with social integration, participation in home and leisure activities, and QoL after TBI (Thomas et al., 2015). However, for many individuals, finding and maintaining a job are difficult due to the sequelae of TBI and various contextual factors serving barriers to community integration (Ciccia & Threats, 2015; McNamee, Walker, Cifu, & Wehman, 2009; Sherer et al., 2014; Whiteneck et al., 2004). Difficulties with RTW often cause financial hardship, forcing many individuals with TBI to rely on benefits from the social security system as their main source of income (Thomas et al., 2015; Kersel, Marsh, Havill, & Sleigh, 2001) and on social support from family and friends (Carew & Collumb, 2008). As deficits related to TBI may become apparent only later in the recovery process for many individuals with TBI (Schönberger et al., 2011), diminished employment outcomes may then be encountered not until then (Cattelani, Tanzi, Lombardi, & Mazzucchi, 2002). Moreover, long-term follow-ups beyond a decade postinjury have demonstrated that vocational status tends to decrease over time, with individuals having difficulties in maintaining steady jobs for prolonged periods (Ashley, Persel, Clark, & Krych, 1997; Hoofien et al., 2001; Kreutzer et al., 2003; Ponsford et al., 2014; Possl, Jurgensmeyer, Karlbauer, Wenz, & Goldenberg, 2001).
Consistent with similar studies, Study I suggests that productivity for measuring participation in work-related activities after TBI is an appropriate outcome variable for the assessment of TBI rehabilitation. The major difference between the treatment and control groups in Study I was due to the fact that more treated than control patients were engaged in productive activity. This is likely to be a direct result of the special rehabilitation program in which patients who would otherwise engage in no productive activity are provided with some means of establishing productive activity. This difference (and the corresponding reduction in the number of patients engaged in no productive activity) suggests that a major impact of the program is on patients at the lower end of functional recovery. However, productivity is a rather broad criterion compared with, for example, gainful work. When return to gainful work was considered in Study I, the difference between the two groups was not statistically significant. It is noteworthy that three of the 11 controls who were in gainful work reported significant difficulties related to their working, and two had less demanding work than before their injury. These findings suggest that successful outcomes need to be expanded to include the ability to engage in a sufficiently wide range of activities.

In CHRPs, the length of the initial intensive remedial phase of treatment which is typically followed by supported work trials and support therapies differs substantially ranging from six weeks in the INSURE program to 20 weeks in other programs (Ben-Yishay et al., 1987; Christensen et al., 1992; Holleman, Vink, Nijland, & Schmand, 2018; Prigatano et al., 1984). Most programs provide 4–5 hours of treatment, for 3–5 days a week. Furthermore, when patients complete a treatment cycle, 50–60% are typically recommended for a second treatment cycle, another 20% proceed to work trials with careful monitoring until they are considered employable, and the rest may be discharged to continue studies or work in their residential areas (Diller & Ben-Yishay, 2003). However, in the INSURE program recommendations to attend it for a second time are not included in the procedures.

Another main difference in the structure of the INSURE program compared with the other CHRPs, is that it is an inpatient program. In the INSURE program, prolonged collaboration of TBI patients with a peer group during their stay at the rehabilitation center may intensify its impact, thus being a crucial component if the CHRP is shortened in length. The context of multidisciplinary rehabilitation has showed up to influence outcomes after ABI (Turner-Stokes et al., 2015). A systematic review by Turner-Stokes and colleagues (2015) including two RCTs provided strong evidence in support of the use of a milieu-oriented approach in moderate to severe TBI, whereby comprehensive neuropsychological rehabilitation is conducted in a therapeutic environment with peers facing similar
challenges. Furthermore, there is some evidence that precisely inpatient expert multidisciplinary rehabilitation may lead to additional gains in outcomes (Turner-Stokes et al., 2015). The INSURE program has been developed to be reasonable in cost, length, and effectiveness taking into account the overall national healthcare and rehabilitation reimbursement system to be a flexible component that can be used as a specific part of the continuum of rehabilitation and management (Kaipio et al., 2000).

The importance of individual and peer group psychotherapeutic interventions that help patients attain optimal psychosocial adjustment and be productive has been emphasized in CHRPs for TBI (NIH Consensus Conference, 1999; Ben-Yishay et al., 1987 and 1985; Christensen et al., 1992; Kaipio et al., 2000; Prigatano et al., 1986). Above all, the psychotherapeutic process is vital for helping patients to achieve a sense of identity, learn to behave in their own best self-interests, and reconstruct life after brain injury. As outlined by McGlynn (1990) and Prigatano (2003), but rarely discussed in the rehabilitation literature, the quality of the therapeutic relationship plays an important role in every type of non-pharmacological treatment. A patient who does not trust or respect the rehabilitation therapist will be unlikely to cooperate, and thus, will not benefit as much as a patient in a good therapeutic relationship. In the book Clinical Neuropsychology and Cost Outcome Research edited by Prigatano and Pliskin (2003), Prigatano referred to INSURE and noted that individual psychotherapy may be a key component in allowing the CHRP to be shortened in length for some patients with TBI.

Cognitive remediation is another essential element of CHRPs (NIH Consensus Conference, 1999; Ben-Yishay et al., 1987, 1985; Christensen et al., 1992; Kaipio et al., 2000; Prigatano et al., 1986). In the Cognitive group of the INSURE program, computerized cognitive training (CCT) has been systematically used (Koskinen & Sarajuuri, 2004). Evidence from systematic reviews (Cicerone et al., 2000, 2005, 2011, 2019; Bogdanova, Yee, Ho, & Cicerone, 2016; Sigsmunddottir, Longley, & Tate, 2016; Velikonja et al., 2014) recommend the use of CCT within a multimodal therapist-guided rehabilitation for cognitive deficits in ABI. The role of the therapist in CCT is to enhance insight into cognitive strengths and weaknesses, to promote compensatory strategies, to facilitate the application of compensatory strategies and generalization of skills from the intervention tasks to everyday life, and to help the patient to process emotional reactions (Tsaousides & Gordon, 2009). CTT allows repetitive cognitive exercises, which are considered to harness neuroplasticity and induce reinforcing or restoration of the defected cognitive function and strengthening the cognitive reserve (Cramer et al., 2011; de Giglio et al., 2016; Han, Chapman, & Krawczy, 2018; Jak, Seelye, & Jurick, 2013; Jolles, van Buchem, Crone, & Rombouts, 2013).
Computerized cognitive training has become an area of increasing popularity due to availability of high-quality, accessible and user-friendly CCT programs and easy implementation in the clinical setting (Kiran, Des Roches, Balachandran, & Ascenso, 2014; Koskinen & Sarajuuri, 2002b; Sigmundsdottir et al., 2016; Walton, Mowszowski, Lewis, & Naismith, 2014). Recent advances in information and communication technology have contributed to the development of innovative tools and improved applications for cognitive rehabilitation, including the use of mobile systems, enriched virtual environments, and commercially available gaming systems to provide remote rehabilitation services, which can clearly broaden service delivery and opportunities for rehabilitation research (e.g. Larson, Feigon, Gagliardo, & Dvorkin, 2014; Tsaousides & Gordon, 2009; Walton et al., 2014).

A rapid step down to no adequate maintenance support has been found to have a negative impact on the durability of the rehabilitation outcome after discharge (Ben-Yishay et al., 1987; Jones & Evans, 1992; Prigatano, 2000; Sander, Kreutzer, & Fernandez, 1997). A recent Cochrane Collaboration intervention review (Turner-Stokes et al., 2015) also reported evidence for that those with moderate to severe brain injury benefit from routine follow-ups to examine their needs for rehabilitation services. In the review, Turner-Stokes and colleagues highlighted that brain injury is for life and rehabilitation results long term are most successful when support and supervision are available on an ongoing basis.

After completion of the basic rehabilitation program, 16 of the 19 patients in the treatment group of Study I continued neuropsychologic rehabilitation according to their rehabilitation plans for the continuation devised in the INSURE program. Eight patients engaged in therapy at the end of the follow-up. One patient continued therapy for 18 months and four patients for a year after finishing the basic program. The effect of subsequent support was not attempted to be separated from that of INSURE because it was considered to be a part of the program.

When assessing applicants for the INSURE program, it should be borne in mind that it is beneficial only for members of particular selected subgroups and not for all people who have sustained TBI. However, the basic principle of learning to cope with TBI can be applied generally in the rehabilitation of injuries that have a wide range of complications and severity. Evaluating the CHRP outcomes, a systematic review by Cicerone and colleagues (2000) found also evidence that participation selection variables, particularly the capacity to become aware, accept and adapt to residual limitations, compliance with treatment objectives, and active participation in treatment may all moderate the effectiveness of CHRPs. The appropriate timing of the CHRP approach seems to be crucial to achieving a positive outcome hence, results in patients with acute
TBI have been associated with less favorable outcomes (Prigatano, 2000; Salazar et al., 2000). Moreover, from a clinical perspective, identifying the subgroups most likely to benefit from different kinds of therapies would allow more judicious allocation of resources optimizing outcomes over the course of recovery (NIH Consensus Conference; 1999, Dikmen et al., 1995; Maas et al., 2017).

Emerging evidence indicates cost-efficacy of rehabilitation after TBI, suggesting that long-term cost savings would exceed short-term rehabilitation costs (Turner-Stokes, 2007; Turner-Stokes et al., 2016). The common concern about CHRPs has been their cost (Wilson, 1997) because they are intensive in treatment hours, number of staff members, and length. This concern translates into related questions concerning the intensity and duration of rehabilitation required for optimal outcomes. High intensity and low staff-to-patient ratio of CHRPs have been suggested to be prerequisites for formulating, implementing, and monitoring the short- and long-term goals in a coordinated manner to meet the desired outcomes (Diller & Ben-Yishay, 2003). This proposal is supported by new findings emerging from the updated review by Turner-Stokes and colleagues (2015) suggesting that multidisciplinary rehabilitation, including specialist neurological rehabilitation services, improves outcomes in adults with ABI and that more intense rehabilitation is more likely to promote faster and possibly improved recovery. Influenced by financial realities, an interesting application of the CHRP approach is a community-based low-intensity, long-term holistic neuropsychological rehabilitation model developed by the publically funded North Wales Brain Injury Service with its local academic partner, Bangor University (Coetzer et al., 2018). Running in postacute rehabilitation settings, central to this clinical model is the relevance of time over intensity of intervention to work towards psychological adjustment after ABI. One of the key components in the model is the provision of long-term psychotherapeutic follow-up.

Eventually, a balance must be attained between the costs of providing the programs while pursuing the outcomes and likely expense savings achieved. Turner-Stokes (2004) has noted that the evidence for cost-efficacy might be gathered from studies, including a cost analysis, or from a secondary analysis of study outcomes, the expenses of which can be calculated, such as independence in daily life or RTW activities. Following a CHRP in Denmark, Larsen and colleagues (1991) reported on healthcare savings in which the program recouped its investment within three years of completion. Study I together with other before-and-after evaluations of CHRPs (Ben-Yishay et al., 1987; Christensen et al., 1992; Cicerone et al., 2008; Klonoff et al., 2001; Prigatano et al., 1984 and 1994) have demonstrated that a majority of the previously unproductive patients were able to obtain participation in work-related activities in some capacity as a long-term and cost-effective psychosocial outcome. However, as Prigatano
(2003) noted regarding psychotherapy after brain injury, some benefits, such as having a meaningful existence and reexperience joy in life, cannot be valued with economic markers.

5.2 CLINICAL RELEVANCE OF INTERRELATEDNESS OF COGNITIVE AND MOTOR FUNCTIONS REGARDING MULTIDISCIPLINARY COMPREHENSIVE REHABILITATION IN TBI

Analyses of the relationships between the neuropsychological and motor performance tests in Study II showed associations between the speed of complex information processing and attention (TMT and Digit Symbol tests) and performance time in agility (running a figure-of-8). Moreover, patients with normal performance in the measures of executive functioning (verbal fluency and reproduction of rhythmic structures) produced a faster mean performance time in tests of dynamic balance and/or agility (tandem walking forwards/backwards and running a figure-of-8) than those with abnormal executive functioning. Thus, fluency of information processing and executive functioning was reflected in the speed of walking and running, and vice versa. Motor functions of the hands (simple and complex forms of praxis) also correlated with the results of all motor performance tests except static balance. These findings concur with those reported earlier that state that measures of information processing, attention, and executive functioning may be associated with locomotor behavior (Cantin et al., 2007; Parker, Osternig, Lee, Donkelaar, & Chou, 2005; Valeé et al., 2006). Cantin and coworkers (2007) found that during locomotor activities TBI participants walked more slowly, had higher clearance margins, and had longer reading times in the Stroop tasks (Lezak, 2004) than healthy participants, indicating attentional inflexibility and slower information processing in TBI patients. Furthermore, significant relationships were observed between scores on the TMT B (test of attention, complex information processing, visual conceptual, visuomotor tracking, and cognitive flexibility) and clearance margins among people with TBI, but not among healthy participants. According to the authors, this may have been the result of poor planning ability because the TBI patients who performed poorly on the TMT B test showed higher clearances over obstacles in complex environments. These findings support the hypothesis that certain measures of cognitive functioning may help to predict motor performance following TBI.

The patients in Study II had difficulty in maintaining static balance on both the right and left legs. Furthermore, 41% had difficulty while simultaneously marching and clapping hands to the slow rhythm, and the fast-rhythm
coordination task gave problems to an even larger proportion of patients (62%).
These findings are in line with those indicating that balance and more complex
motor tasks involving coordination are common deficits after TBI (Basford et al.,
2003; Campbell & Parry, 2005; Geurts et al., 1996; Geurts et al., 1999; Lehman
et al., 1990). The strong effect of slow- versus fast-rhythm coordination tasks
on patients’ performance identified in Study II suggests that the relation of motor
to cognitive task performance may be due to a common underlying factor, namely
speed of processing, consistent with Study II’s general finding. This, in turn,
suggests the important clinical implication that the impact and compensation
for slowed processing speed across cognitive, motor, and functional tasks should
be addressed in an integrated CHRP approach. An example of this would be to
incorporate an intervention that aims to reduce disabilities arising from mental
slowness or slow information processing due to ABI within both cognitive and
physical interventions. Such an intervention would be, for instance, time pressure
management (TPM) as a compensatory cognitive strategy training (Ylvisaker,
Szekeres, Henry, Sullivan, & Wheeler, 1987) based on (1) the view that slowed
processing is not very amenable to restitution, but requires a compensatory
approach, and (2) that TPM is supported by the scientific evidence (Cicerone et al.,
2019; Winkens, Van Heugten, Wade, Habets, & Fasotti, 2009). The essence of the
TPM method is that patients learn to give themselves enough time to deal with
time pressure in the information processing of the task at hand (Fasotti, Kovacs,
Eling, & Brouwer, 2000). Having identified slowed processing as a central aspect
of dysfunction or functional limitations in Study II, an alternative approach would
be a CHRP in which all therapies address processing speed from within their
own framework and perspective as part of cognitive and physical interventions.
Overall, the CHRP approach should be flexible in incorporating multiple, distinct
interventions shown to be effective in addressing the myriad of specific deficits
after TBI.

Tandem walking tests were used to measure dynamic balance in this study, and
the performance time was associated with the measures of executive functioning.
As a consequence, the performance time in the balance test turned out to be
more revealing than the balance control per se (performing the test without side
touches or mistakes in tandem steps). The time measure in the tandem walking
test has not generally been considered so important earlier. However, measuring
the time may bring a whole new dimension to the evaluation via the identified
link to information processing and executive functioning.

The finding of Study II that the motor functions of the hands correlated
with almost all motor performance tests may be due to the fact that the motor
component was rigorously tested. Moreover, the tests of hand motor functions
included simple and complex forms of praxis, reflecting executive functions and
their role in producing voluntary movements. The hand praxis correlated with all of the motor performance tests, except static balance, which may also indicate the importance of the executive component in the motor functions in question.

Study II showed no significant correlation between the reproduction of rhythmic structures and rhythm coordination on the motor side. Some interaction might have been expected based on the regulation of motor acts, which is needed in both tasks for producing voluntary movements. One reason for the absence of a correlation may be differences in the content and demands for regulation between the two tasks: reproducing rhythms from a pattern presented acoustically vs. marching on the spot in synchrony with a metronome signal and clapping the hands.

Serrien and colleagues (2007) have attempted to model the neural processes recruited during complex motor tasks. During well-learned motor skills, a network comprising primary and secondary sensorimotor cortical areas, and subcortical regions are engaged. Cognitive resources are recruited during the acquisition of complex skills and when external and internal factors are altered. Cognitive resources ensure that an action is performed in accordance with the goal requirements and that the frontal-lobe systems linked to response selection and monitoring are engaged. In line with the model, the findings of Study II showed in practice that cognitive processes are related to motor processes. Although the significance of such processes is generally accepted, their underlying mechanisms and interaction with motor circuits are far from clear.

Apart from the theoretical relevance of Study II, the finding of an association between cognitive and motor performance may potentially have clinical relevance to the field of neurorehabilitation. No causation can be assumed, although consistent with compelling evidence in adult populations of various ages and health statuses (Carruthers, Zampieri, & Damiano, 2014; Colcombe, & Kramer, 2003; Guiney, & Machado, 2013; Pensel et al., 2018; Sanders, Hortobagyi, la Bastide-van Gemert, van der Zee, & van Heuvelen, 2019), accumulating evidence from the few studies investigating the causal relationship has suggested that physical activity and interventions may improve cognitive functioning after TBI, even in the chronic stage (Carruthers et al., 2014; Chin, Keyser, Dsurney, & Chan, 2015; Damiano et al., 2016; Grealy et al., 1999; Thornton et al., 2005). Following a training program on an exercise bicycle, Grealy and colleagues (1999) reported significant improvements in learning and speed of information processing as well as in movement times and reaction times in TBI patients. More recently, Chin and colleagues (2015) reported that after an aerobic training program on a treadmill, significant improvements in cognitive function were observed in processing speed, aspects of executive functioning, and overall cognitive function in individuals with TBI. Moreover, gains in cardiorespiratory fitness were
strongly related to the magnitude of cognitive improvements (Chin et al., 2015). Likewise, Damiano and colleagues (2016) found positive effects after a cross-training program on learning, depression, sleep quality, and motor processing time demonstrated in faster balance reaction times, walking and high-level mobility performance in chronic TBI. The change scores across domains after training were strongly associated, which the authors interpreted to support the multimodal effects of training in TBI. Physical exercise has been hypothesized to work as an adjunct for cognitive interventions, given that exercise increases serum levels of neurotrophic factor, which has been related to cognitive functions (Carruthers et al., 2014). Additionally, a recent meta-analysis (Perry, Coetzer, & Saville, 2018) found up to a medium effect size of physical exercise on reducing depressive symptoms in individuals with TBI, consistent with meta-analyses in non-TBI populations (e.g. Lauzé et al., 2018; Vargas-Terrones et al., 2019; Verrusio et al., 2018). A meta-analysis by Carruthers and colleagues (2014) on effects of cognitive interventions on motor function in humans identified no studies in the TBI population. Overall, this literature in humans is very limited and findings are inconsistent in demonstrating positive effects on motor function (Carruthers et al., 2014), partly due to commonly used motor-related outcome measures of low sensitivity such as ADL performance. It has been suggested that cognitive training may indirectly potentiate motor function by improving resources in the brain that allow motor functions to be executed more effectively (Carruthers et al., 2014).

Collectively, recent research has provided evidence that cognitive and motor domains are more interrelated than previously thought (Carruthers et al., 2014). Relationships between cognitive and motor function are a potentially important area of further research with clinical implications on neurorehabilitation strategies. Along with effects of exercise on cognitive function, future research should explore in more detail the effects of cognitive training on motor function. Another important question for future studies with potential clinical implications on neurorehabilitation is whether combining physical exercise with cognitive interventions would facilitate better cognitive outcomes than cognitive interventions alone.

Combining therapeutic cognitive and motor activities may approximate the demands of everyday life more closely than artificially separating them in distinct therapy sessions. For rehabilitation to be successful, it is crucial to address problems from multiple perspectives and to foster comprehensive and transdisciplinary teamwork (NIH Consensus conference, 1999). This suggestion is in line with the earlier thinking of Goldstein in the 1940s and 1950s (1941, 1948, 1951 and 1959) and more recently Ben-Yishay (1996, p 333) about the
important elements of CHRPs, such that: “... remedial interventions in head-injured individuals cannot and should not be artificially partitioned, nor should they be carried out in isolation from one another, as purely physical, or cognitive therapies, or (conventional) psychotherapy ...”. Although CHRPs are oriented neuropsychologically, they are also multidisciplinary. However, physical activities in CHRPs have presumably thus far been primarily provided for the pleasure of physical exercise and joy of mastery of the body as well as to encourage patients to engage in sporting activities to enhance condition. Current research has highlighted the new dimension of including physical activities in multidisciplinary neurorehabilitation via the identified interplay between motor performance and cognition and benefits of physical exercise on cognitive functioning and mood.

5.3 SUBJECTIVE APPRAISALS OF OBJECTIVE OUTCOMES AFTER COMPREHENSIVE-HOLISTIC REHABILITATION

Based on Study I outcome findings, Study III explored the relationship between objectively measured outcomes of neurorehabilitation and their subjective self-appraisal by patients with TBI who had resumed working in various levels of competence following CHRPs. The main finding of Study III was that for persons with TBI after CHRPs, the levels of work and the subjective self-appraisals were not associated in areas other than the self-appraised ability to establish intimate relationships. Overall, patients’ self-ratings for areas of well-being were generally quite high following CHRP, including the ability to establish intimate or closely acquainted relationships, which had nevertheless the lowest self-rating.

Given that the majority of subjective self-rated outcomes and the vocational outcome showed no significant relationship, our findings are consistent with previous studies that have noted a dissociation between functional outcomes and subjective well-being, especially in patients with chronic TBI (Bezner & Hunter, 2001; Cicerone et al., 2004; Koskinen et al., 2011). By contrast, Ben-Yishay and colleagues (2010) reported that the level of work competence that was attained was associated with the sum of self-appraisals in patients with TBI who had undergone a CHRP. This unpublished, cross-cultural pilot study (Ben-Yishay et al., 2010) involved 201 patients with TBI from ten countries. The patients had resumed working in some capacity for a minimum of six months following a CHRP. The same objective and subjective outcome measures were used as in Study III. According to the unpublished report, results showed that the patients’ self-ratings correlated with the objectively assessed outcomes of their rehabilitation. However, the report does not include in the methods section
an explanation of the statistical analyses used, instead referring to a table presenting \( P \) values of the Spearman rho correlations among the sum of the six self-appraisal ratings. The table does not present any correlation coefficients, OR, or CI ranks for the \( P \) values. Due to these methodological shortcomings, it is difficult to interpret the reliability and validity of the study findings.

In Study III, the identified inconsistency between the level of work (sheltered workshop or volunteer, subsidized work, and competitive work) and self-appraised well-being (effort during rehabilitation, meaning in life, productivity, acceptance, social life, and the ability to establish intimate relationships) may be due to the fact that in the CHRPs the patients have individually tailored placements and supported work trials that help them to find productive activities that suit their abilities and interests after TBI (Cicerone et al., 2011; Prigatano, 1999; Sarajuuri et al., 2005). The effort directed to achieving consistency between the capabilities of the patients and the requisites of the work or other productive activities seems to be crucial in enhancing well-being. RTW as such has not been shown to guarantee good psychosocial adjustment (Sander et al., 1997). Moreover, O’Neill and colleagues (1998) suggested that part-time employment might be superior to full-time employment after TBI. In their study, part-time workers had fewer unmet needs, were more socially integrated, and were more engaged in activities at home than their full-time peers. Full-time workers may have been so fully engaged in their work that they had less time and energy to pursue other life domains. An important finding is also been reported that individuals with TBI who return to work-related activities before they are ready may show more difficulties with adjustment, heightened stress, and maladaptive strategies over time, which may jeopardize their employment (Ownsworth & Oei, 1998; Sale, West, Sherron, & Wehman, 1991; Stocchetti & Zanier, 2016). These findings suggest that successful outcomes for productivity are related to the compatibility between resources and capabilities of the patients after injury.

Study III showed a dissociation between functional outcomes and subjective well-being, suggesting that community functioning and the related satisfaction are distinct aspects of participants’ experience that must be considered in the evaluation of rehabilitation for TBI patients. The findings imply that the relationship between objective indices of functional outcomes and subjective well-being is moderated by subjective meanings and values assigned by patients. Moreover, the findings confirm the increasing awareness that outcome assessments need to be supplemented by subjective, experiential measures that reflect the patient’s own perspective and guide improved clinical management after TBI (e.g. Ben-Yishay & Daniels-Zide, 2000; Dijkers, 2004; von Steinbuechel et al., 2012). The incongruity of the relationship between objectively measured outcomes and their subjective appraisals has implications for the targeting of
rehabilitation interventions and poses a challenge for outcome measurement. Ben-Yishay and Daniels-Zide (2000) have highlighted that conventional approaches of viewing outcomes as parameters of self-care, ambulation, speech, or ability to perform work-related tasks ignores the bigger picture of rehabilitation and also deprive professionals of a meaningful way to determine if and when the brain-injured person has reached full rehabilitation potential. By looking at how the patients view their inner world, it is possible to develop meaningful ways of measuring how far patients have come in realizing their potential for making functional and subjective adjustments for their disabilities (Ben-Yishay & Daniels-Zide, 2000).

Most of the patients (53%) in Study III attained part-time competitive employment, and about one-third (31%) attained subsidized or volunteer work ability. Notably, only 13% attained full-time competitive employment, only one of whom resumed in a job for which he had received academic training preinjury (as the most demanding level of work on the 10-point scale). RTW rates overall are highly variable across the literature. Despite advances in critical care and rehabilitation methods, changes in disability legislation, and increasingly important economic reasons, research has consistently documented that RTW rates remain low after TBI (van Velzen et al., 2009; West, Targett, Crockatt, & Wehman, 2013). According to a systematic review of RTW studies conducted by van Velzen and colleagues (2009), on average approximately 40% of patients with TBI achieve RTW at some level at both one and two years after injury, and notably, a substantial proportion were unable either to return to their former work or to return permanently. A systematic review of RTW by Saltychev and colleagues (2013) also did not yield strong evidence that vocational outcomes after TBI could be predicted or improved. As a result of a variety of cognitive, behavioral, and emotional disorders, impaired psychosocial, physical, and sensory functioning, and medical symptoms, individuals who sustain TBI often experience difficulty in becoming competitively employed postinjury and in maintaining employment (Artman & McMahon, 2013; Keyser-Marcus et al., 2002; Saltychev et al., 2013; van Velzen et al., 2009).

Study III identified the ability to establish intimate relationships to be the only area of subjective self-appraisals that were associated with the levels of work. The procedure to verify associations between the levels of work and the subjective self-appraisal of the areas of wellness following rehabilitation showed that the skewness of the distribution of the self-appraisals did not have an effect on the results, and the ability to establish intimate relationships remained the only area of self-appraisal to have a significant association with the level of work attained. That is to say, the higher the attained work ability (sheltered workshop or volunteer, subsidized work, and competitive work), the better the self-rated
ability to establish intimate relationships. In addition, the lowest subjective self-ratings in Study III were related to the ability to establish intimate or closely acquainted relationships. These observations may be clinically important at a number of levels. Keeping a job and handling higher level responsibilities often means getting along with people and understanding their needs as well. Research on TBI and employment is full of examples of emotional dysregulation, behavioral problems, and lack of awareness of one’s deficits being particularly disabling with regard to achieving and maintaining gainful employment (Artman & McMahon, 2013; Gill et al., 2011). These factors have also been perceived as barriers to relationships, particularly intimate ones, after TBI (Gill et al., 2011). Mood swings, irritability states, and unpredictable patterns of behavior have been shown to impose the greatest strain on personal relationships (Williams & Evans, 2003; Wood et al., 2005). Neurobehavioral and emotional problems, which may be the major challenge for facing rehabilitation and for enhancing efforts at community adjustment, intimate relationships, productivity, and overall well-being in life after TBI (Morton & Wehman, 1995), should be addressed by rehabilitation interventions more thoroughly.

The patients in Study III were in a quite chronic phase, the mean time from TBI to evaluation being nearly ten years (mean±SD: 9.7±5.5 years; range: 4.0–36.0 years) but had not succeeded in resuming work before the CHRPs. This note supports the previous findings that outcomes after TBI are not time bound and that individuals living with moderate to severe TBI can show improvement of functional outcomes many years after injury and benefit from a long-term health-management approach (Maas et al., 2017; Wilson et al., 2017). Overall, in Study III, the patients with TBI were found to be largely satisfied with the areas of wellness (effort during rehabilitation, meaning in life, productivity, acceptance, social life, and intimate relationships) in their lives even years after CHRPs. These findings support the assumptions underlying CHRPs that they facilitate achievement of a successful outcome through the establishment of a meaningful and satisfactory life after TBI in the face of persisting limitations (Ben-Yishay & Daniels-Zide, 2000; Cicerone et al., 2008; Prigatano et al., 1994).

5.4 EVALUATION OF STUDIES I–III

There are some limitations of the studies that must be considered when interpreting the findings. Study I was not an RCT, which weakens the conclusions. In the Cochrane Database of Systematic Reviews, Turner-Stokes and colleagues (2015) highlighted that all questions in rehabilitation for ABI cannot be addressed by RCTs or other experimental approaches. Rehabilitation
is a complicated intervention that has many interrelated and interdependent components, and its benefits typically incur over several years. As an implication for future studies on rehabilitation, they suggested gathering practice-based evidence from long-term cohort studies conducted in the context of routine clinical practice (Turner-Stokes et al., 2015). In Study I, an attempt was made to evaluate the outcome of one form of rehabilitation conducted in a clinical rehabilitation environment after a two-year follow-up compared with a matched control group receiving conventional clinical care and rehabilitation. For objectivity of the outcome evaluation, two neuropsychologists, who were not in any other way involved in this study or in patients’ care and rehabilitation and who were blinded to the rehabilitation that each patient had received independently assessed patients’ productivity statuses by analyzing the questionnaires. As a result, the consistency of the classification of patients into productive and nonproductive categories by the two blind raters was perfect.

In a matched-control study design, groups should be carefully compared on important variables to rule out alternative explanations. On average, the study groups were very similar regarding each of the important variables shown to impact outcome and measured in the preinjury and acute phases. The possible confounders were taken into account in statistical analysis, and neither the demographic variables nor the injury-related variables confounded the role of the rehabilitation program in the outcome evaluation. Time since injury of the participants was on average three and a half years during which they had received conventional clinical care and rehabilitation without achieving productivity, which may have controlled spontaneous recovery and strengthened the effect of the present intervention. However, we did not select the control patients to match patients in the treatment group with respect to their pretreatment productivity, although they were similar concerning their preinjury productivity. Study I was also limited by its small sample size, which affects the generalizability of the findings.

Moreover, in Study I, we did not address detailed information about the rehabilitation of control patients. The aim of the study was to evaluate the outcomes of patients who underwent a special rehabilitation program and to compare these outcomes with those of patients who received the conventional clinical care and rehabilitation available in the healthcare units. The type of rehabilitation that the treatment group received before the INSURE program reflects the conventional rehabilitative care of the control patients. However, additional research is needed to evaluate the contents and benefits of different rehabilitation interventions.

After its publication, Study I has been included in systematic reviews and meta-analyses with rigorous methodological selection criteria on the effectiveness of
rehabilitation for people with TBI (Cicerone et al., 2011; Geurtsen, van Heugten, Martina, & Geurts, 2010; Tsaousides & Gordon, 2009; Turner-Stokes, 2008). A meta-analysis (Cicerone, Azulay, & Trott, 2009) on the methodological quality of research on rehabilitation after TBI reported four high-quality observational studies, including Study 1, that support the effectiveness of CHR after TBI with improvements in psychosocial outcomes, the other studies being those by Cicerone and colleagues (2004), Goranson and colleagues (2003), and Rattok and colleagues (1992).

Recently, Zaninotto and colleagues (2018) conducted a systematic review of the literature through the Web of Science database by searching the keyword ‘traumatic brain injury’ in articles titles, organized the data of the articles included in the review according to the CONSORT 2010 criteria, and analyzed the 100 most cited high-quality TBI trials in order to provide methodological recommendations for designing future trials in TBI. Study I was included in these trials and was also among the 27% of these that were procedure or device trials. Only sixteen of these, including Study I, were related to some type of rehabilitation program or behavioral intervention. By contrast, most (42%) of the remaining studies investigated the effects of drugs.

The limitations of Study II that should be acknowledged are as follows. Firstly, the study was conducted among men, and generalization to women with regard to the evaluation of motor performance requires caution. In general, men are at higher risk of TBI (the risk to men is 0.88–2.5 times higher than that to women; Cassidy et al., 2004). Secondly, the patients with TBI were fairly heterogeneous with respect to GCS scores (range: 3–15) and types of CT/MRI findings. On the whole, they seemed to have recovered well physically, which was consistent with the inclusion criteria. Thirdly, the representativeness of the results is limited by the small sample size. Nevertheless, the number of patients was sufficient for reliable explorative statistical analysis and the results can be interpreted as indicative. Studies examining the relationship between cognitive and motor performance in TBI patients have been scarce, although research in this field has captured recent interest through the potential important clinical relevance and implications to neurorehabilitation.

Considering the limitations of Study III, the sample size of the study was relatively small affecting the generalizability of the findings. In addition, the study did not include a control group. Nevertheless, the primary purpose of Study III was not to assess the effectiveness of holistic neurorehabilitation, but to explore whether objectively measured successful outcomes of rehabilitation and the participants’ subjective self-appraisal of these outcomes are associated. Moreover, the measure to assess the patients’ subjective self-appraisal in postrehabilitation outcomes in six areas (effort during rehabilitation, meaning
in life, productivity, acceptance, social life, and intimate relationship) (Ben-Yishay et al., 1987; Ben-Yishay & Daniels-Zide, 2000), has not been evaluated regarding its reliability and validity. However, this tool was chosen and regarded as justifiable since it was directly relevant and suitable for the questions being addressed and earlier literature has relied on it for formulation of research questions. Furthermore, the specific aim of Study III was to re-examine the conclusions of Ben-Yishay and collaborators (2010) who used the same tool to examine the relationship between objective and subjective rehabilitation outcomes. While developing the tool, Ben-Yishay and Daniels-Zide (2000) stressed that in contrast to previous indicators of self-appraisal focusing on pathological aspects of experience, such as anxiety, anger, and depression, the notion of self-appraisal as a metric in defining rehabilitation outcomes with positive connotations has been requested and also taken into account in the further development of QoL measurers (Koskinen, Hokkinen, Wilson, Sarajuuri, von Steinbuechel, & Truelle, 2011; von Steinbuechel et al., 2012; Truelle et al., 2010). However, additional research is needed to evaluate the contents and benefits of different rehabilitation interventions. This study included participants who had resumed working at various levels of competence following rehabilitation. In future studies, it would be interesting to explore how patients with different objective outcomes, or patients who have not attained ability to participate in work-related activities after rehabilitation, rate their subjective well-being or QoL.

The strengths of Study III include, the same CHRP approach being conducted in two different rehabilitation centers located in different countries and the results for both countries being consistent supports their generalizability. Moreover, Study III utilized a combined measure to investigate TBI outcome after rehabilitation, which allowed two outcome domains and their associations to be examined. Although it has become increasingly evident that that outcome assessment of TBI should be multidimensional to show treatment effects (Honan et al., 2019; Kean & Malec, 2014; Maas et al., 2017; Wilde et al., 2010), this approach has not been used in the majority of TBI outcome studies (Humphreys et al., 2013). Composite instruments for measuring outcome after TBI are required, with only diverse individual outcome measures currently being available (Kean & Malec, 2014; Maas et al., 2017). Further work is needed to develop composite outcome assessments to guide improved clinical management after TBI.
5.5 CONCLUSIONS

Extending over a period of 15 years, the outcome study of the thesis (Study I) was one of the first to include a control group in this context. The results of Study I support the proposition of previous cohort studies that were conducted without concurrent controls and the few comparative studies at that time suggesting that CHRP with adequate postdischarge maintenance therapy and ongoing support can improve psychosocial functioning in terms of productivity in patients with moderate to severe TBI even years after the injury. Since then, the effectiveness of CHRPs delivered in therapeutic milieus by a collaborative multidisciplinary team, in close collaboration with the patient and family, in enhancing psychosocial outcome and adjustment, resulting in less emotional stress and greater self-esteem of individuals with TBI has been supported by growing evidence from additional comparative studies (Hashimoto et al., 2006; Svendsen & Teasdale, 2006), an RCT (Cicerone et al., 2008), and systematic reviews (Cattelani, Zettin, &Zoccolotti, 2010; Cicerone et al., 2011, 2019; Geurtsen et al., 2010; Tsousides & Gordon, 2009; Turner-Stokes, 2008) on multidisciplinary TBI rehabilitation. Thus, there seems to be substantial evidence to conclude that CHRPs represent an effective approach for patients requiring neuropsychologically oriented multidisciplinary rehabilitation following moderate to severe TBI.

In line with the few previous studies, the findings of Study II support the interplay between cognition and motor performance and suggest that measures of information processing, attention, and executive functioning may be associated with motor performance. Apart from the theoretical relevance, these findings may have clinical relevance for rehabilitation. The interrelatedness between cognitive and motor performance supports the possible multimodal effects of TBI rehabilitation and encourages use of multidisciplinary CHRP to enhance outcomes after TBI. Recent related studies have also proposed a possible causal relationship, demonstrating that physical activity may improve cognitive functioning after TBI, even in the chronic stage (Chin et al., 2015; Damiano et al., 2016), and supported the proposition of the multimodal effects of physical training in TBI (Damiano et al., 2016). Moreover, combining therapeutic cognitive and motor activities may approximate the demands of everyday life more closely than artificially separating them in distinct therapy sessions. If rehabilitation is to be successful, it is crucial to address problems from multiple perspectives and to foster comprehensive and transdisciplinary teamwork (NIH Consensus Conference, 1999). This is in accord with the earlier proposals of Goldstein (1941, 1948, 1951, 1959) and Ben-Yishay (1996) about the important elements of CHRPs.
In Study II, the performance time in the dynamic balance test was associated with the measures of executive functioning. In preceding studies, the time measure in the evaluation of dynamic balance has not generally been considered to have great importance (e.g. Basford et al., 2003; Geurts et al., 1996). However, in Study II, the performance time in the balance test was more revealing than the balance control per se in the results. This finding suggests that measuring the time may bring a whole new dimension to the evaluation of dynamic balance via the identified link to information processing and executive functioning. Moreover, the findings imply that the relation of motor to cognitive task performance may be due to a common underlying factor, namely speed of processing. This, in turn, suggests the important clinical implication that the impact and compensation for slowed processing speed across cognitive, motor, and functional tasks should be addressed in an integrated CHRP approach. Overall, the CHRP approach should be flexible in incorporating multiple, distinct interventions shown to be effective in addressing the myriad of specific deficits after TBI.

Finally, the results of Study III support the need to evaluate rehabilitation outcomes involving both objective outcome measures and subjective measures of patients’ evaluations of the objective outcomes. The present results indicate that community functioning and related satisfaction are distinct aspects of participants’ experience that must be considered in the evaluation of rehabilitation following TBI. Given that the majority of subjective self-rated outcomes and the vocational outcomes showed no significant relationship, the results of Study III are consistent with previous studies that have noted dissociation between functional outcomes and subjective well-being, especially in chronic TBI. In Study III, patients with individually tailored placements and supported work trials that helped them to find productive activities to fit their capabilities and interests after TBI were largely satisfied with the areas of wellness in their life. Matching the capabilities of patients and the requisites of work-related activities seems to be crucial for enhance successful productivity outcomes and well-being – return to work as such was not shown to guarantee good psychosocial adjustment in the long run.

The results of Study III also indicated that the ability to establish intimate relationships was the only area of self-appraisal to have a significant association with the level of work attained following CHRPs. The self-rated ability to establish intimate or closely acquainted relationships had also the lowest self-rating for the TBI patients. Keeping a job and handling higher level responsibilities often means getting along with people and understanding their needs as well. The present findings support previous ones suggesting that neurobehavioral and emotional problems may actually be the major challenge for facing rehabilitation and for enhancing efforts at community adjustment, intimate relationships, productivity, and overall well-being in life after TBI.
Thus, rehabilitation interventions should consider addressing neurobehavioral and emotional problems more extensively to improve outcomes after TBI.

Overall, the results of this thesis give evidence that the CHRP approach does overcome handicaps and improve outcomes for individuals with moderate to severe postacute TBI (Studies I and III). These findings support the presumption underlying CHRPs that they facilitate achievement of a successful outcome through establishing a meaningful and satisfactory life after TBI in the face of persisting limitations. Additionally, supporting the previous findings, outcomes after TBI are not time bound and individuals living with a moderate to severe TBI can show improvement of functional outcomes many years after injury. Interrelatedness of cognitive and motor functions (Study II), in turn, supports the possible multimodal effects of TBI rehabilitation and speaks in favor of comprehensive multidisciplinary neurorehabilitation. These findings may have implications for rehabilitation service provision and allocation, largely encouraging movement towards CHRP models in rehabilitation of individuals with TBI to enhance their psychosocial outcomes and well-being.


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APPENDIX A: ORIGINAL PUBLICATIONS
APPENDIX B

Scale for scoring preinjury and postrehabilitation work competence (Ben-Yishay & Diller 2006) for Study III

<table>
<thead>
<tr>
<th>Description</th>
<th>Weighted Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resumed full-time (competitive) compensated work in job for which the subject received academic training pre-injury</td>
<td>10</td>
</tr>
<tr>
<td>Resumed part-time employment only as above</td>
<td>9</td>
</tr>
<tr>
<td>Attained full-time competitive employment in a clerical or skillful work capacity acquired by on-the job training post rehabilitation</td>
<td>8</td>
</tr>
<tr>
<td>Attained part-time competitive employment only as above</td>
<td>7</td>
</tr>
<tr>
<td>Attained full-time subsidized work ability (in any area)</td>
<td>6</td>
</tr>
<tr>
<td>Attained part-time subsidized work ability only as above</td>
<td>5</td>
</tr>
<tr>
<td>Attained full-time volunteer (i.e. non-compensated) work ability</td>
<td>4</td>
</tr>
<tr>
<td>Attained part-time volunteer work ability (only)</td>
<td>3</td>
</tr>
<tr>
<td>Attained work ability in a sheltered workshop (only)</td>
<td>2</td>
</tr>
<tr>
<td>Attained no work ability even in a sheltered workshop</td>
<td>1</td>
</tr>
</tbody>
</table>